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SHEARING OF NERVE FIBRES AS A CAUSE OF BRAIN DAMAGE DUE TO HEAD INJURY

A Pathological Study of Twenty Cases

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THIS paper is not about concussion nor about lacerations or contusions of the brain, but about the fact that, as Gama put it in 1835, " fibres as delicate as those of which the organ of mind is composed are liable to break as a result of violence to the head ".

Although head injury is the most common cause of neurological disorders in this country, remarkably little is known about the pathology of brain damage in this condition. There are various reasons for this. Only a few brains from patients with acute head injuries or post-traumatic neurological signs reach the hands of neuropathologists (and when they do they are often difficult to study because they have been so mishandled). Because it is tedious to examine a brain histologically, pathologists have been content to study the damage visible to the naked eye—such as lacerations or coup and contre-coup lesions (Lindenberg and Freytag 1960)—which, though interesting, are often not the cause of the patient's death or even of his neurological signs. Experimental workers, on the other hand, have been so fascinated by the problem of concussion, which is supposed to be either fatal or completely reversible (i.e., to leave no structural changes) that they have usually tried to avoid producing obvious brain damage in their experiments.

In 1956 I reported the pathological changes in the brains of five patients who had received apparently uncomplicated head injuries and yet had remained in a state of extreme dementia, with severe neurological abnormalities, until they died many months later. The main finding was a severe and widespread degeneration of the white matter of the brain, the grey matter being almost unaffected. My purpose now is to report a further fifteen cases of this condition.

Fig. 1—Coronal section of brain of patient who survived for 6 weeks.
Note that the only abnormal appearances are slight dilatation of the ventricles and a tear (arrow) on the underside of the corpus callosum to the right of the midline. This type of lesion was present in all twenty cases.

Clinical Features

The twenty patients under discussion (including the five already reported) were remarkably similar both clinically and pathologically. Most of them were young, and almost all were injured in road accidents. Only two had fractures of the skull. There were no lacerations of the brain, and no significant intracranial hæmorrhages, nor was there any evidence of raised intracranial pressure. Blood-pressure, pulse, and respirations were normal at the first examination except in a few who were temporarily shocked because of other injuries. All the patients were unconscious from the time of the accident, and when first seen they responded only to painful stimuli, often with generalised extensor spasms—the so-called " decerebrate " or " brain-stem attacks ". Their limbs were spastic and often more severely paralysed on one side than the other. The neurological signs did not change much over the weeks, though the mental state of the patients who survived long enough improved to some extent. They would lie with their eyes open for much of the day, and they appeared to sleep for the rest of the time. They could easily be roused from sleep, though even when awake their reactions to the environment were very limited. They could cough, chew, and swallow, and they followed sounds and moving objects with their eyes. Many were able to speak a few words and to obey commands, but only one (case 2) improved enough to be able to leave hospital, though he never became normal.

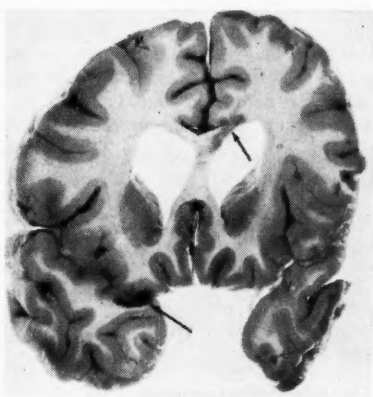

Fig. 2—Coronal section through the brain of the first case (survival for 1 year).
The only obvious abnormalities are a lesion on one side of the corpus callosum (arrow), a cortical contusion (arrow), and moderate ventricular dilatation. The white matter looked normal to the naked eye, but shows severe degeneration microscopically (fig. 11).

Postmortem Findings

When the brains were examined lesions visible to the naked eye were few and inconspicuous (figs. 1 and 2). The blood-vessels showed no atheroma. Some degree of generalised ventricular dilatation was present, but there was no cortical atrophy and the white matter looked normal. There was some atrophy of the thalami. A few small contusions, minute softenings, and occasional punctate areas of yellowing (old hæmorrhages) could be seen in the hemispheres and brain-stem. These hæmor-

Fig. 3—Section through upper pons of same case as in fig. 2, showing the typical lesion (arrow) due to tearing, in the superior cerebellar peduncle.

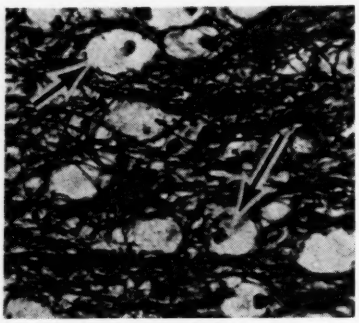

Fig. 4—White matter from the first case, showing many fat-granule cells (arrows) lying among normal-looking surviving nerve-fibres (Glees silver stain × 515).

rhages were often found under the ependyma and at the junction of cortex or basal ganglia with the white matter. All cases had had hæmorrhages into the corpus callosum and twelve had similar lesions in one or both superior cerebellar peduncles (figs. 1, 2, and 3). Many blocks were taken from each brain and frozen, paraffin, and celloidin sections were examined using the usual neuropathological stains, including the Marchi method. The degeneration in these cases tends to be greatest deep in the brain, and it can therefore be overlooked if blocks of cortex with little underlying white matter only are taken. Slight lesions may be very difficult to see, and the easiest way of demonstrating them is by the Marchi method. This was originally designed to stain the products of acute myelin breakdown and it has to be modified for staining long-standing degeneration (Smith, Strich, and Sharp 1956, and Smith 1956).

Fig. 5—Marchi preparation of spinal cord (× 2·5) of the same case as in fig. 11.

Despite bilateral hemisphere damage (visible only microscopically) note that only one pyramidal tract, crossed and uncrossed, is degenerated.

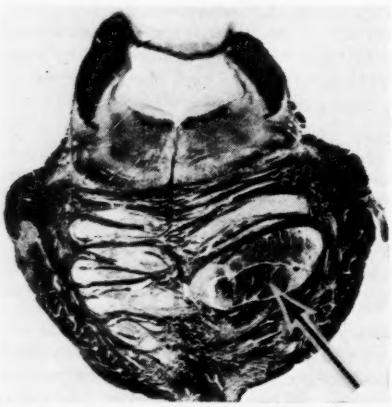

Fig. 6—Section through the pons of the second case, showing marked degeneration of the descending tracts on the right, those on the left (arrow) being normal (myelin × 2·5).

Slight damage to the other long tracts shows up in a Marchi preparation but is not readily seen in a section stained for myelin, such as this.

Histological Changes

The results of the microscopic examination were startling. It was found that there had been a widespread diffuse degeneration of the white matter characterised, in the long-surviving cases, by large numbers of fat-granule cells (phagocytic cells containing the fatty products of myelin breakdown) lying among apparently normal nerve-fibres, which were much reduced in number (fig. 4). Fibrous gliosis was absent, or only slight. The same histological picture of degeneration was seen in fibre bundles such as the anterior commissure, the fornix, and the corpus callosum. In the brain-stem ascending and descending tracts were similarly affected, often in a strikingly asymmetrical manner despite degeneration of the white matter in both hemispheres (figs. 5 and 6).

The appearances strongly suggested secondary or wallerian degeneration, but no obvious focal lesions were found to account for the interruption of the nerve-fibres except in the corpus callosum and superior cerebellar peduncles. In cases with shorter survival (up to 6 weeks) active myelin and nerve-fibre degeneration was seen and there were large numbers of nerve-fibres with retraction balls—evidence that the fibres had been severed (figs. 7, 8, 9, and 10). (When a nerve-fibre in the peripheral or central nervous system is cut, axoplasm flows out of both cut ends and is visible as a large blob. These structures were first described and named retraction balls or clubs by Cajal [1928]).

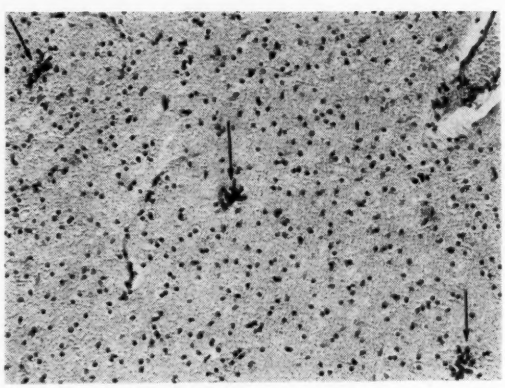

Fig. 7—5 or 6 weeks after the injury numerous glial stars or knots (arrows) are seen in the white matter (Nissl × 140).

Fig. 8—A typical retraction ball on the end of a nerve-fibre, from a patient who survived for 10 days (Bielschowsky silver impregnation × 570).

This contains a vacuole, as illustrated by Cajal in his original description of retraction balls.

Apart from the few small lesions seen macroscopically, the cerebral cortex appeared normal. This does not mean that it was actually normal, for most neuropathologists agree that it is impossible to detect cell loss until it has reached the order of 33–50%. I am certain, however, that what cell loss there may have been was not enough to account for the degeneration in the white matter which, in thick sections stained by Marchi's method, was gross enough to be plainly visible to the naked eye (fig. 11). There were changes in the thalamus secondary to the nerve-

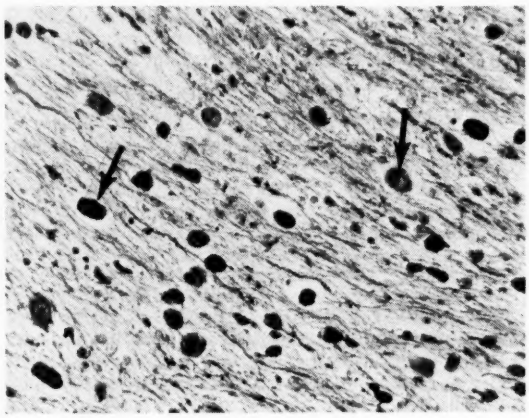

Fig. 9—A bundle of the internal capsule of the third case (survival for 24 days). (Holmes silver impregnation × 235).

The large blobs are the retraction balls (arrows to two) which form at the ends of severed nerve fibres. Fragmented and degenerating axons can also be seen.

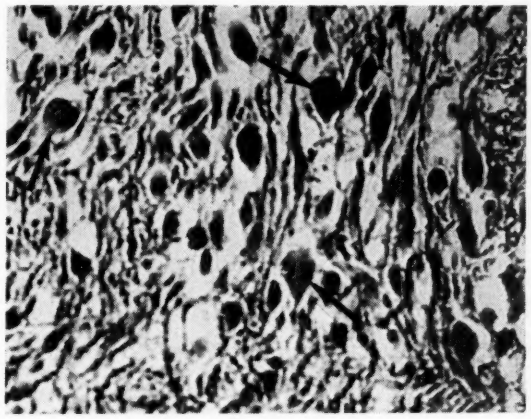

Fig. 10—Retraction balls from a patient who survived after a head injury for 48 hours (hæmatoxylin and eosin × 430).

These structures (arrows), though most conspicuous in silver stained preparations, can be seen in all the routine stains.

fibre loss, and gliosis was present in some of the brain-stem nuclei. The nerve-fibre degeneration in the white matter and the long tracts accounted for the neurological signs and the mental state of the patients.

Representative Case-reports

THE FIRST CASE

Extreme Dementia and Quadriplegia, with 12 months' Survival (Maudsley no. 754)

A 17-year-old boy fell 30 feet from a crane and was unconscious immediately. Examination within the hour showed that he was still unconscious, responding only to painful stimuli, mainly with extensor spasms. The pupils were small and equal, and reacted normally. Both legs were rigid; tone in the arms was normal, and he moved them spontaneously. Systolic blood-pressure varied between 50 and 100 mm. Hg. He was bleeding from the right ear and the pharynx, the right side of the chest contained fluid; there was hæmaturia. X-rays of the skull showed a right parietal linear fracture. He was given a transfusion of three pints of blood, and a tracheostomy was made the same evening. During the next few days he had several bouts of fever (up to 104°F); the hæmaturia stopped. 10 days after the accident he was still unconscious, his pupils and eye movements were normal, there was no facial weakness, and swallowing and gag reflexes were present. Motor power was less on the right, and the tendon reflexes were increased on that side. Both plantar responses were extensor. He responded to painful stimuli applied to all parts of the body.

4 weeks after the accident he responded to sound and moved more purposefully. 2 weeks later he lay with open eyes, blinked, and had coordinated eye movements, looking towards the site of any stimulation and following sounds and moving objects. He could swallow semisolids if fed slowly. He appeared to sleep at times and he could be roused from this state. There was no further improvement over the months. He had several attacks of pneumonia, bedsores eventually developed, and he died a year after the accident.

Necropsy

The body was very emaciated, with the left arm extended in the decerebrate posture, the right adducted and flexed. The brain weighed 1210 g. (fixed).

Macroscopic examination of the brain.—Old yellow contusions were present on either side of the left sylvian fissure, on the tips of both temporal lobes, and on the under aspect of the left frontal lobe. The pons was shrunken. Coronal sections showed considerable ventricular dilatation especially of the frontal horns (fig. 2). The cortex was of normal thickness except in the areas of old contusions. The white matter looked normal. There were old hæmorrhagic softenings in the body of the right caudate nucleus, in the corpus callosum more on the left than the right, and in both superior and cerebellar peduncles, right more than left. Both thalami were atrophied. There were a number of pinpoint yellow areas in the tegmental region of the mid-brain, and the cerebral aqueduct was dilated. There were small areas of yellowing in the superior vermis of the cerebellum. The pyramids were not shrunken but they looked chalky white.

Microscopic examination.—There was severe symmetrical white-matter degeneration in the cerebral hemispheres (fig. 11), with relative sparing of the frontal poles and the temporal lobes. In the occipital lobes there were only slight changes in the white matter generally, but the external and internal sagittal strata (which carry association fibres) were markedly

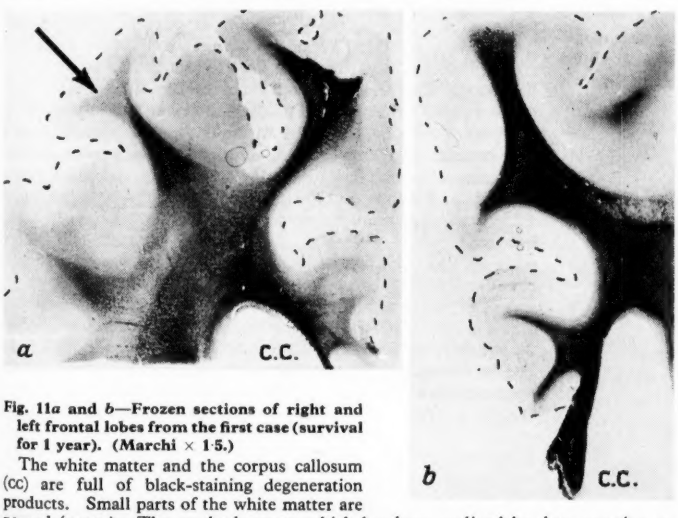

Fig. 11*a* and *b*—Frozen sections of right and left frontal lobes from the first case (survival for 1 year). (Marchi × 1·5.)

The white matter and the corpus callosum (CC) are full of black-staining degeneration products. Small parts of the white matter are normal (arrow). The cerebral cortex, which has been outlined by dots, contains no Marchi-positive material.

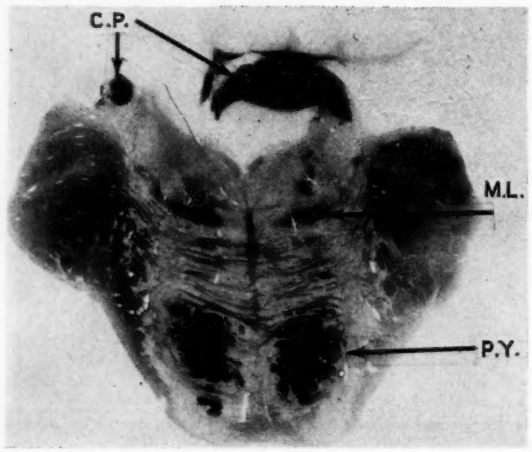

Fig. 12—Section through pons of the first case (1 year survival) in which the degenerated tracts appear black (Marchi × 2·3).
P.Y. = pyramidal tract, C.P. = superior cerebellar peduncles, M.L. = medial lemniscus.

involved. The corpus callosum and the fornices had been partially interrupted by hæmorrhagic softenings, and the internal capsules and the stalks of the thalami contained many fat-granule cells. There were cortical contusions on either side of both sylvian fissures, with cell loss in the adjacent gyri, and parts of the Sommer's sector of both Ammon's horns had been destroyed; otherwise the cerebral cortex looked normal. Severe cell loss and gliosis were seen in both thalami, presumably secondary to the interruption of their afferent and efferent connections. There was a slight generalised gliosis in the white matter, most marked under the contusions and at the corticomedullary junction. In the brain-stem symmetrical degeneration of the corticospinal fibres, the medial lemnisci, the central tegmental tracts, and both middle and superior cerebellar peduncles was seen (fig. 12). A tiny old hæmorrhage in one substantia nigra, and a small peri-aqueductal glial scar, were the only focal lesions found. The cerebellum showed generalised Purkinje-cell loss, particularly in its upper half, with complete sclerosis of some folia.

THE SECOND CASE

Dementia, Hemiplegia, and Ataxia, with Partial Recovery and Accidental Death 2 years later (Maudsley no. 866)

A boy, aged 14, was involved in an accident and was unconscious immediately. On admission to hospital he had right frontal and left temporal scalp lacerations, and a right frontal depressed fracture without laceration of the dura. He responded to painful stimuli; both legs and the right arm were spastic, and

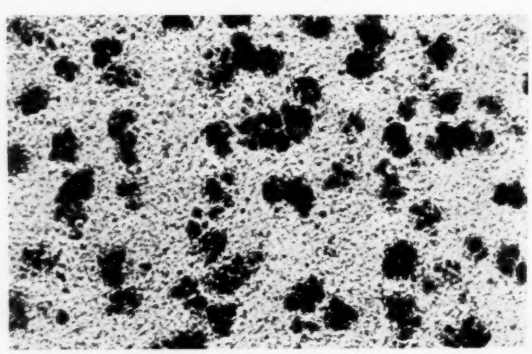

Fig. 13—Frozen section of white centrum semiovale of the second case (survival for 2 years), showing Marchi-positive products of de eneration in fat-granule cells (Marchi × 235).

he had a left hemiparesis. Shortly after admission he had a generalised convulsion lasting 30–60 seconds, and during the next few days he had several more fits involving the left arm and the left angle of the mouth. Because lung infection gave rise to anxiety, a tracheostomy was made. Lumbar puncture on the 5th day showed slightly bloodstained fluid, at a pressure of 220 mm. water. Ventriculography 3 weeks after the accident showed slight symmetrical ventricular dilatation.

He improved slowly. On the 10th day he began to open his eyes and to make more purposeful movements with his right arm. Tube feeding was discontinued in the 7th week and the tracheostomy was closed. He began to speak and to obey commands after 10 weeks, and it became clear that he had severe ataxia of the right limbs as well as a left hemiparesis. 12 weeks after the accident he was apathetic and disorientated, though alert; and he was still doubly incontinent. His speech was slurred and monotonous. 5 months after the injury he was sent home. Attempts were made to get him back to school; but the considerable residual physical disabilities, together with antisocial behaviour and great difficulty in concentration, made this very difficult. He died from drowning 2 years after the original accident.

The Brain at Necropsy

There were two circular bony defects in the frontal region. The brain weighed 1450 g. A subdural membrane, up to 0·1 cm. thick, was found in the right frontal region overlying a cortical contusion in the right superior frontal convolution. Small contusions were also present in the left superior frontal convolution. Coronal sections showed slight ventricular dilatation, greatest in the right anterior horn. There were a few punctate and linear areas of yellowing in the white matter, including the splenium of the corpus callosum. There was one cortical infarct at the bottom of a sulcus in the right occipital lobe. The right side of the pons and the right pyramidal tract were smaller than the left.

Microscopic examination.—White-matter changes were only moderate or slight in the central white matter, but they were more intense in the internal capsules, particularly in the posterior limbs and the retrolenticular parts. The fronto-parietal regions and the right occipital lobe were the most severely affected. The white matter of the temporal lobes was spared, but here there was patchy cell loss in the third layer of the cortex, and occasional very small scars. There were lesions in Ammon's horn on both sides. The sagittal strata of both occipital lobes, including part of the visual radiation, showed much degeneration; there was corresponding gliosis in the centre of both lateral geniculate bodies. Cell loss and gliosis were present in other nuclei of the thalamus, left more than right, with degeneration of afferent or efferent connections. There was a softening about 0·3 cm. in diameter between the right substantia nigra and the basis pedunculi. In the lower brain-stem degeneration was severe in the right descending tracts, moderate in the right medial lemniscus and left superior cerebellar peduncle, and slight in the left medial lemniscus and the central tegmental tracts (fig. 6). There was some generalised Purkinje-cell loss in the cerebellum, and incomplete sclerosis of the folia on the upper surface of the right, and the under surface of the left, lobes. In all the affected areas in both hemispheres and brain-stem there were fat-granule cells laden with Marchi-positive material (fig. 13). There was also a little round-cell cuffing of the vessels, and some astrocytic gliosis.

The presence of so much residual fatty material is interesting, and it is impossible to know how much had been removed in the 2 years since the accident. The asymmetry of the tract degeneration in the brain-stem is noteworthy (see later). Lesions of the optic radiations are not uncommon in these cases.

THE THIRD CASE

Extreme Dementia, with Quadriplegia, Wallerian Degeneration, and numerous Retraction Balls, and with 24 days' Survival (Maudsley no. 49/57).

An eccentric man, aged 66, who was partially blind and deaf, was knocked down by a car, and became unconscious im-

mediately. On examination half an hour later he responded feebly to pain, and the pupillary reactions were normal; tendon reflexes were sluggish but equal. Bitemporal burr-holes were made on the 3rd day, and small subdural hygromata were evacuated without clinical improvement. 6 days after the accident he responded to shouts by grunting, the right arm was paretic, and there was variable spasticity in all limbs. He died without improvement 24 days after the injury.

The Brain at Necropsy

No fractures of the skull were found, and the brain weighed 1300 g. The cortex portruded slightly at the site of the burr-holes. The blood-vessels at the base of the brain were normal. Coronal sections showed moderate ventricular dilatation. There was a fairly recent tear in the left side of the corpus callosum, and a hæmorrhage in the head of the left caudate nucleus, encroaching on the anterior limb of the internal capsule. Brain-stem and cerebellum looked normal.

Microscopic examination.—The picture was most dramatic in sections in which the axons had been impregnated with silver. Many areas showed fragmented, bulbous, or tortuous nerve-fibres, and in many places large numbers of retraction balls could be seen (fig. 9). Breaking-up myelin with phagocytosis by microglia could also be seen. Retraction balls, although most conspicuous in silver preparations, can easily be seen in hæmatoxylin and eosin preparations (pink) as in fig. 10, or in hæmatoxylin and van Gieson preparations (yellow). Often small groups or bundles of nerve-fibres had been damaged, and in many areas it seemed that fibres running in one direction only had been interrupted, so that the retraction balls and swollen axons looked like shoals of fish. Many of the Betz cells of both motor cortices showed chromatolysis. Small lesions were present in the anterior commissure and the fornices. In the brain-stem the long tracts on the right were much more severely affected than those on the left.

Pathogenesis of the Lesions

The evidence available at present strongly suggests that nerve-fibres are torn or stretched at the time of the accident, and that this is the cause of the degeneration found post mortem. The evidence has already been discussed in detail (Strich 1956), but it can be summarised here. It is typical of these cases that gross and permanent neurological signs appear *immediately* after the impact. One patient, for instance, whose accident was witnessed by a trained nurse, took up her characteristic posture with both legs and the right arm rigidly extended, and the left arm flexed, as soon as she hit the ground. The injury to nervous tissue must therefore be immediate. This rules out œdema, anoxia, vascular disturbances, and fat-embolism, the effects of which take time to develop, but it is consistent with sudden widespread damage to nerve-fibres. Direct evidence of such tearing is provided by the presence, in early cases, of numerous retraction balls at the ends of the interrupted nerve-fibres. Furthermore, the changes both in the white matter of the cerebrum and in the long tracts of the brain-stem and spinal cord are typical of the secondary or wallerian degeneration which follows interruption of nerve-fibres from any cause. The histological appearances are not those of œdema, which is characterised by the absence of fat and the presence of fibrous gliosis, nor of anoxia, which mainly affects the grey matter. Some of the lesions seen, for instance the gross tears in the corpus callosum and the superior cerebellar peduncles, are obviously due to mechanical trauma.

It was pointed out by Holbourn (1943, 1945), a physicist, that a substance with the physical properties of brain is likely to be damaged by shearing forces. Brain substance, like the cerebrospinal fluid in which it floats, is highly incompressible—i.e., great pressure is required to alter its size. This means that the brain cannot rattle about in the skull. On the other hand the brain is very easily altered in shape or distorted, for instance by rotation of the skull about any axis. Thus, when the head is given a sudden twist, parts of the brain (as well as the meninges and cerebrospinal fluid) shift relative to each other, and the stresses and strains set up by this movement are enough to tear nerve-fibres, synapses, and even blood-vessels. Such damage was predicted by Holbourn. He also said (1943, and personal communication) that since the hemispheres are not exact replicas but mirror images of each other it is to be expected that under certain conditions (i.e., when the brain is rotated in any of its planes of symmetry) nerve-fibres running in a particular direction would be selectively damaged in one hemisphere and spared in the other, the quantity of damage being the same on the two sides. Such asymmetrical degeneration—for example of the corticospinal fibres, the optic radiation, or the medial lemniscus in the brain-stem—was in fact found in many of our cases (figs. 5 and 6). It provides striking confirmation of Holbourn's theoretical prediction, and otherwise is inexplicable.

When present, the foci of yellowing, representing old hæmorrhages, were often found where the consistence of the brain changes—e.g., under the ependyma, or at the junction of the white matter and cortex or basal ganglia. In such areas one would expect shear strains to be greatest.

There is much clinical evidence that rotation of the head affects the brain in head injuries. It is possible to produce concussion, and even decerebrate rigidity and death (Paul 1957), by rotating the head with a blow. Conversely it is well known that boxers, including fair-ground-booth pugs, can tolerate severe direct blows to the head provided their neck muscles are strong and they can keep their heads still (O'Connor 1957). For the same reason men can head footballs with impunity.

Experimental evidence for the importance of head movement was first provided by Denny-Brown and Russell (1941), who showed that it requires less force to produce concussion in cats when the head is free to move than when it is fixed. Failure to realise this and the fact that the shearing strains set up during rotation are less the smaller the brain (Holbourn, personal communication), accounts for the difficulties which experimental workers have had in producing brain damage in small animals, which usually develop permanent neurological signs only after repeated blows to the head. Under such circumstances, however, nerve-fibre degeneration has been seen in the spinal cord by Schmaus (1890), and in the brain by Jakob (1913), Tedeschi (1945), Windle (1948), and others. Direct evidence that the brain does not draw away from the skull when subjected to mechanical forces, but shifts and swirls if the head is free to move, even with subconcussive blows, was provided by Pudenz and Shelden (1946), using high speed cinematography on monkeys whose skull caps had been replaced with transparent material.

Tedeschi (1945), Groat et al. (1945), Windle et al (1944, 1945), and Groat and Simmons (1950) also found damage to nerve-cell bodies particularly in the brain-stem, and it is not suggested here that injury to nerve-fibres is the only way in which the nervous system may be affected by a head injury. Apart from lacerations due to penetrating wounds or gross intracerebral hæmorrhages, I have seen cases in which cerebral œdema played an important role in the failure to recover after injury, particularly in patients

with subdural or extradural hæmatomata. I have also seen a number of cases with large areas of necrosis or innumerable small grey-matter infarcts, which were clearly due to vascular disturbance, and there may be other pathogenetic factors.

The white-matter degeneration here described was found post mortem in twenty of forty-three patients who had been severely incapacitated as a result of head injury. No estimate of the real incidence of nerve-fibre damage can be given, however, because these cases were highly selected and not enough acute ones have been examined. Only severe examples of the condition are reported here, but there is every reason to suppose that lesser degrees occur in patients with trauma to the head whether the skull is fractured or not. It also seems possible that if nerve-fibres are stretched rather than torn, the lesions may be reversible at some stage, and may play a part in the production of the signs of concussion.

Historical Survey

This can be short. The only other report of a case of severe white-matter degeneration (with tears in the corpus callosum and one superior cerebellar peduncle) comparable to ours is that of Rosenblath (1899); he examined the brain of a 17-year-old tightrope walker who, after a fall survived in a " sleep-like state " for 8 months. The lesions were thought to be due to a particularly severe form of concussion.

Summary

Diffuse severe degeneration of the white matter of the brain may follow a closed and apparently uncomplicated head injury, leaving the patient permanently incapacitated, and more or less demented. The pathological findings in twenty cases surviving after head injury for 2 days to 2 years are used to illustrate this condition.

Evidence is presented that the extensive white-matter lesions, both of hemisphere and brain-stem, represent a secondary degeneration of nerve-fibres which have been stretched or torn by the shear stresses and strains set up during rotational acceleration of the head at the time of the accident.

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ERYTHROPOIETIC PROTOPORPHYRIA

A NEW PORPHYRIA SYNDROME WITH SOLAR URTICARIA DUE TO PROTOPORPHYRINÆMIA

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Of the known diseases affecting porphyrin metabolism, only porphyria congenita (Günther's disease) is regarded as being due to an abnormality of the hæmopoietic system. All others are thought to be expressions of a disturbed pyrrole-pigment metabolism in the liver, as indicated by the classification proposed by Schmid, Schwartz, and Watson (1954). Photosensitivity, which appears as a symptom of congenital erythropoietic porphyria, may be present in the cutanea tarda and " mixed " hepatic types.

Recent observations on two patients with porphyria cutanea tarda by Magnus, Porter, and Rimington (1959) showed that abnormal reactivity of the skin was restricted to a narrow region in the spectrum around 400 mμ. This is the site of most intense absorption of energy by the porphyrin molecule. Immediate erythema followed by swelling two to three hours after exposure, and lasting three to four days or longer, was produced experimentally. Ecchymoses and subsequent atrophy were also observed in these patients when they were exposed at this wavelength. Such reactions were similar to those produced in the two porphyric subjects mentioned above by natural exposure to radiation. The close correspondence between the action spectrum thus obtained and the absorption spectrum of porphyrins, all of which show an intense absorption band—the Soret band—in the 400–410 mμ region was taken as indicating that their porphyrins were responsible for the photosensitivity of these patients.

We now report a case of porphyria, with light sensitivity of a type we believe not to have been described before. The presenting symptom was solar urticaria. Quantitative irradiation of the patient showed that his skin was most sensitive in the 400–410 mμ spectral region, but the reaction differed from that encountered in patients with porphyria cutanea tarda in that there was prompt erythema and wealing instead of delayed œdema. Despite this difference, a diagnosis of porphyria was entertained and confirmed by the finding of greatly increased fæcal coproporphyrin and protoporphyrin excretion. The urinary porphyrin was normal. In an effort to throw further light upon the unusual reaction to irradiation, the blood was examined for porphyrins. None could be detected chemically in plasma on the first occasion, and only a small amount of protoporphyrin during a second examination when the patient was extremely sensitive to artificial irradiation; but, on each occasion, the red cells were found to contain grossly abnormal amounts of protoporphyrin and coproporphyrin. The unusual reaction to light is thought to be related to the high content of these porphyrins in the circulating erythrocytes.

That the metabolic abnormality was referable to the erythropoietic system was eventually demonstrated by detection of numerous red-fluorescent normoblasts in a

smear of sternal bone-marrow viewed in the ultraviolet fluorescence microscope. Intoxication by lead has been excluded.

Preliminary reports of the case have already been made elsewhere (Magnus 1961a and b).

Case-report

A male restaurateur, aged 35, first consulted one of us (I. A. M.) in 1960, complaining of swelling on the skin after exposure to sunlight. This had happened for twenty-seven years, the swellings being preceeded by intense itching, and arising within five minutes of exposure. They lasted for about half an hour, after which some erythema remained. All the skin surface was susceptible, but the normally covered areas reacted more vigorously. The condition was worst during the summer, but it also arose on sunny winter days. Artificial light had not been noticed to produce symptoms.

General health had been good, except for vague abdominal discomfort and colic for about ten years. Cholecystectomy was performed in 1955, and a solitary gallstone was found; the gallbladder was histologically normal. His symptoms did not change after this operation.

Family history was negative.

Clinical investigation.—Physical examination was essentially normal; the liver and spleen were not enlarged, nor was there clinical evidence of anæmia or jaundice. There was no hyperpigmentation, hirsuties, erythema, conjunctival suffusion, telangiectasia, or atrophy. Nor was there any abnormal fragility of the skin.

Special Investigations

Light Tests

Tests were made by exposing areas of skin of the patient's back to measured doses of various wavelengths of light. For this purpose a powerful quartz-xenon monochromator was used, delivering selected narrow wavebands (Magnus et al. 1959). In March, 1960, an abnormal wealing response was obtained between 360 and 450 mμ. At 400 mμ five minutes' exposure caused a weal, whereas normally in this band over sixty minutes is required to produce merely erythema. Exposure to narrow wavebands centered at 360 and 450 mμ caused immediate erythema and itching but no wealing. Other spectral regions—e.g., 260–320 mμ produced normal erythemal responses, whereas at 450–900 mμ there were no visible reactions. These findings indicated the possibility of some disturbance of porphyrin metabolism.

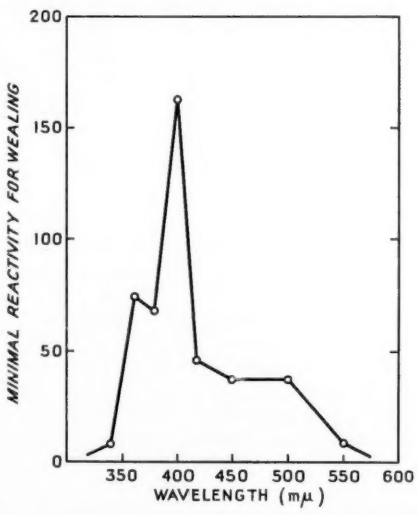

Fig. 1—Action spectrum for wealing (December, 1960).
The ordinate scale—minimal reactivity for wealing—is the reciprocal of the minimal dose required to produce wealing. This dose of radiation is expressed in arbitrary units—i.e., t (time in seconds) × I (intensity). Intensity was measured with a galvanometer and linear vacuum thermopile with quartz window (Hilger, F.T. 17).

TABLE I—SPECIAL INVESTIGATIONS (MARCH, 1960, TO DECEMBER, 1960)

	1960					
	March	April	May	June	July	December
Light sensitivity ..	+++ (5 min.)	..	++ (10 min.)	..	+ (20 min.)	++++ (see fig. 1)
Urine						
(μg. per day):						
Coproporphyrin ..	90	..	32	..	..	56
Uroporphyrin ..	0	..	0	..	..	0
δ-aminolævulic acid	..	..	2000	..	..	2700
Porphobilinogen ..	..	..	2000	..	..	2220
Stool						
(μg. per g. dry wt.):						
Coproporphyrin ..	24	72	26	..	..	11
Protoporphyrin ..	112	105	341	..	..	494
Uroporphyrin ..	..	..	0	..	..	0
Plasma						
(μg. per 100 ml.):						
Coproporphyrin ..	No	No	0	0	..	0
Protoporphyrin ..	fluores-	fluores-	0	0	..	70
Uroporphyrin ..	cence	cence	0	0	..	0
Red cells						
(μg. per 100 ml.):						
Coproporphyrin ..	..	..	10	..	..	7
Protoporphyrin ..	..	..	708	..	..	1332
Uroporphyrin ..	..	..	0	..	..	trace

Further monochromator tests in May, 1960, showed diminished sensitivity. A weal could still be produced with ten minutes' exposure at 400 mμ, but adjoining regions of the spectrum were without effect. Later tests (July, 1960) showed further decrease in skin sensitivity to 400 mμ radiation, twenty minutes' exposure now being required to produce a weal.

In December, 1960, the threshold dose for response was determined at regular spectral intervals to obtain an approximate action spectrum. It was found that the patient's susceptibility to long-wave ultraviolet and visible radiation had greatly increased. The results are depicted in fig. 1, which shows clearly that the maximal spectral reactivity lies at about 400 mμ. The responses to sunburn radiation between 250 mμ and 320 mμ were essentially within normal limits.

Porphyrin Determinations

Repeated urinary, fæcal, and serum porphyrin examinations made between March, 1960, and January, 1961, using standard methods (Rimington 1958) are recorded in table I. Urinary coproporphyrin, porphobilinogen, and δ-aminolævulic acid (Mauzerall and Granick 1956) were well within normal limits, but coproporphyrin and protoporphyrin levels in stool and red blood-cells (Wranne 1960) were consistently and grossly raised. Uroporphyrin was absent except for a trace amount found once in the erythrocytes.

The red-cell protoporphyrin was extracted from 25 ml. of packed cells and converted to mesoporphyrin (Rimington 1938). Paper chromatography by a new technique (to be published), effective in separating mesoporphyrins I and IX, showed the pigment derived from the patient's red cells to be entirely mesoporphyrin IX.

Enzymic production of Porphyrins from δ-aminolævulic acid

Hæmolysates prepared from the patient's red cells and from those of a normal control were incubated with δ-aminolævulic acid and radioactive iron (^{59}Fe) under standard conditions for three hours at 37°C. The porphyrins and hæm formed were determined quantitatively, with the results presented in table II. The coproporphyrin produced in this experiment was examined by paper chromatography and identified as coproporphyrin III only. Although mature human erythrocytes are practically incapable of transforming coproporphyrinogen III to protoporphyrin, and of forming hæm, radioactive iron was included in the experiment in case the patient's cells should prove abnormal. As will be seen from table II, the hæmolysate formed more uroporphyrin than the control, and slightly more new protoporphyrin, but the same amount of new coproporphyrin. The difference between the net protoporphyrin figures is of questionable significance; so also is that between the very low counts of hæm activity. In general, the enzymic

TABLE II—SYNTHESIS OF PORPHYRINS AND HÆM FROM δ-AMINOLÆVULIC ACID IN THE PRESENCE OF ^{59}FE BY HÆMOLYSATES OF THE PATIENT'S BLOOD AND BY A NORMAL CONTROL

Incubation for 3 hours at 37°C.

Synthesis	Control			Patient		
	Initial values	After 3 hours	Amount synthesised (mean)	Initial value	After 3 hours	Amount synthesised (mean)
Uroporphyrin (μg.) ..	0	13·5		0	30·5	
	0	9·3	11·4	0	41·4	36·0
Coproporphyrin (μg.) ..	0	30·8		0·8	31·0	
	0	30·7	30·8	0·8	31·4	30·4
Protoporphyrin (μg.) ..	0·1	3·2		25·5	31·2	
	0·1	3·7	3·3	25·5	31·1	5·7
Hæm (counts per min. per mg. of hæm) ..	..	6·5	..	..	1·0	..
	..	6·8	..	..	1·7	..

activity of the patient's blood did not differ appreciably from that of the control.

Special Hæmatology

A blood-count in June, 1960, showed the following: Hb 15 g. per 100 ml.; red cells 4·8 million per c.mm.; and white cells 5100 per c.mm. (neutrophils 65%; lymphocytes 30%; monocytes 2%; eosinophils 3%; basophils 0%). The red cells appeared morphologically normal, and red-cell fragility was normal.

Serum-iron was 145 μg. per 100 ml., and the unsaturated-iron-binding capacity (in January, 1961) was 240 μg. per 100 ml.

The red-cell survival-time, measured by ^{51}Cr tagging in June-July, 1960, was found to be slightly low, with the half-life 23 days (normal 24–28 days).

Despite the above essentially normal findings, an iron utilisation test was carried out with the object of detecting any possible defect in the incorporation of iron into newly formed protoporphyrin during hæmopoiesis. ^{59}Fe was injected intravenously, and its rate of disappearance from the plasma was measured over the next six hours. This followed an essentially normal logarithmic course (fig. 2). The utilisation of ^{59}Fe in the bone-marrow, and release of labelled cells into the circulation, which occurred during the next ten days also followed a normal pattern (fig. 3); the ^{59}Fe half-life in red cells was 3·1 days. Surface counting of radioactivity over spleen, liver, and bone-marrow sites showed normal patterns of uptake.

Bone-marrow

Bone-marrow biopsy was performed by Dr. Eva Graves in January 1961, when the patient was highly photosensitive. The marrow specimen was very cellular but appeared otherwise normal. Under ultraviolet light, however, numerous red fluorescent normoblasts were seen.

Skin Biopsies

Skin biopsies were taken twice during 1960. The first was in March; skin was removed from the back and examined in the fresh and fixed states for porphyrins by fluorescence microscopy, but no abnormal fluorescence was detected.

In June an urticarial lesion was produced by two minutes' exposure to the quartz-xenon monochromator. The lesion was immediately excised, and frozen sections were examined for porphyrin fluorescence. This examination also failed to reveal any fluorescence due to porphyrins. The histological appearance was compatible with the clinical diagnosis of urticaria.

Urinary Aminoacids

Paper chromatography showed a normal pattern. The creatinine content of a specimen in March, 1961, was 250 mg. per 100 ml.

Blood and Urinary Lead

In view of the known increase of erythrocyte porphyrins in lead poisoning, determinations were made (Dr. R. Allcroft) of lead in the patient's blood and urine. Figures of 0·18 and 0·05 mg. per litre respectively were found; these are within the normal range. Radiography revealed no evidence of deposition of lead in the bones.

Response to Drugs

Chlorpheniramine maleate, 12 mg., taken three hours before exposure to irradiation from the monochromator, appeared to reduce the wealing response at 400 mμ but the effect was not great; the patient claimed that the itching, associated with wealing, was greatly reduced. He was accordingly put on a regular dosage of 16 mg. q.d.s. for four weeks, but this was not very effective and was therefore discontinued. Triamcinolone 4 mg. t.d.s. for two weeks was also tried, but was without significant benefit.

Discussion

From the irradiation tests with the monochromator it seems that this patient's skin is most sensitive to those wavelengths in the region of 400 mμ which are strongly absorbed by porphyrins. His clinical photosensitivity showed fluctuations of intensity which corresponded with quantitative changes in his erythrocyte and fæcal porphyrins; hence it seems justifiable to conclude that the porphyrins produced in his body are responsible for his photosensitisation. In cases of porphyria with photosensitisation, it is often uroporphyrin which is present in greatest excess, and the response to irradiation is by erythema and itching followed by slowly developing œdema, often with blister formation. This man, however, produced *no* abnormal quantity of uroporphyrin but excessive amounts of protoporphyrin which were localised mainly within his circulating red cells. Red-cell coproporphyrin was also raised by about the same multiple above normal levels. These two porphyrins were found in large amounts in the fæces, and during phases of enhanced light sensitivity protoporphyrin was also detectable in the plasma. At no time was the urinary coproporphyrin above normal, and uroporphyrin was consistently absent. The reaction of his skin to light was by immediate erythema, itching, and wealing. Therefore the patient differed

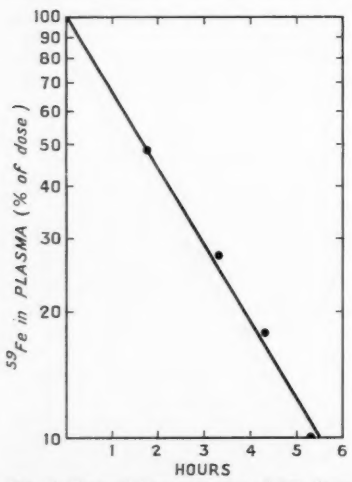

Fig. 2—Rate of disappearance of ^{59}Fe from patient's plasma.

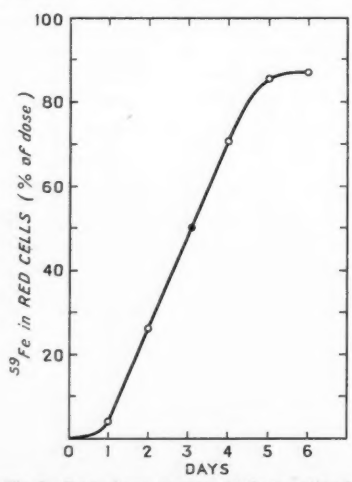

Fig. 3—Rate of appearance of ^{59}Fe in patient's circulating red cells (half-life = 3·1 days).

strikingly from cases of congenital porphyria (Günther's disease) or of porphyria cutanea tarda.

Schmid et al. (1954) have introduced the very useful subdivision of the porphyrias into erythropoietic and hepatic, according to whether the bone-marrow or the liver is the site of the metabolic disturbance of porphyrin metabolism. The only erythropoietic porphyria so far recognised is congenital porphyria (Günther's disease); in this condition massive quantities of series-I porphyrins are formed, uroporphyrin I predominating, and are excreted in the urine and stools. Protoporphyrin levels are little if at all affected. The finding of porphyrin-containing fluorescent normoblasts in our patient's bone-marrow clearly indicates that his porphyria is of erythropoietic type. The porphyrin is mainly protoporphyrin which is of the normal isomeric type (series III). No previous example of such a condition has been described, and we propose to designate it " erythropoietic protoporphyria ".

When seeking to explain the mechanism of this biochemical abnormality, we encounter considerable difficulty. The possibility that it might result from intoxication by lead can be dismissed on account of the normal blood and urine lead contents. No defect in iron utilisation for hæm formation could be demonstrated. The red cells are of normal fragility, and their mean life, determined by ^{51}Cr tagging, is only slightly less than normal. Finally, an in-vitro examination of porphyrin synthesis from δ-aminolævulic acid by a hæmolysate of the patient's red cells indicated enzymic activities which do not differ much from those of a normal subject. There was a greater production of uroporphyrin than in the control flask, but coproporphyrin production was the same.

The capacity to form protoporphyrin from coproporphyrinogen III is normally lost as the human red cell loses its nucleus, and the cells of the peripheral blood are therefore incapable of carrying out this transformation. It seemed just possible that during maturation, the patient's cells might have retained this enzymic capability, thus accounting for their high protoporphyrin content; but the experiment with the hæmolysate showed that this was not the case.

The patient has had his symptoms since the age of 8; both parents are dead and he has no sibs. He has one child, a daughter aged 10, living in Rhodesia, who is said to be normal, and he can recall no known photosensitivity in his family. It is difficult to say, therefore, whether his condition is acquired or is the expression of a unique genetic abnormality.

Summary

Investigation of a patient with light-sensitive urticaria revealed abnormal reaction of his skin to monochromatic irradiation at 400mμ.

His urinary excretion of porphyrin, porphobilinogen, and δ-aminolævulic acid was normal, but stool protoporphyrin and coproporphyrin levels were much raised. The red cells contained greatly increased amounts of protoporphyrin and coproporphyrin; the former was converted into a mesoporphyrin shown by paper chromatography to be mesoporphyrin IX. Levels of blood and urinary lead were not abnormal. Porphyrin production by a hæmolysate with δ-aminolævulic acid as substrate revealed no significant abnormality. Red-cell survival was only slightly less than the normal range. The patient's iron metabolism was normal. The bone-marrow contained numerous fluorocytes, indicating an erythropoietic disturbance of porphyrin metabolism.

Uroporphyrin was not found in abnormal quantity in any situation. The absence of uroporphyrin clearly distinguishes this syndrome from congenital porphyria. It seems to be an hitherto undescribed erythropoietic condition for which we suggest the name " erythropoietic protoporphyria ".

We are grateful to colleagues for help with certain investigations as follows: Dr. Arthur Tickner, of the Institute of Dermatology, for the porphyrin determinations in March and April, 1960; Dr. R. Allcroft, of the Central Veterinary Research Laboratory, for the lead determinations; Dr. E. M. Graves, of University College Hospital, for the general hæmatological examination; and Mrs. A. Latter for help with the porphyrin chromatography and red-cell hæmolysate experiment.

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SOME OBSERVATIONS ON THE MODE OF FORMATION OF OXALATE-CONTAINING URINARY CALCULI

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ABOUT two-thirds of all urinary calculi in man contain calcium oxalate as a major component (Jensen 1941, Prien 1949, Lagergren 1956). In this unit, analysis of 504 urinary calculi by X-ray diffraction has revealed that 69% contained calcium oxalate (B.T. Murphy and M. J. Purton, unpublished results). The factors which lead to the formation of oxalate-containing stones are, therefore, particularly relevant to the problem of stone formation.

An analysis of calcium excretion in relation to stone composition has revealed that abnormally high urinary calcium is most often found among patients with oxalate-containing stones (Cottet and Vittu 1955, Hodgkinson and Pyrah 1958), and it seems that hypercalciuria is ætiologically important in the formation of this type of stone.

We have observed that oxalate-containing calculi can be divided into two broad groups, depending on their gross structure; and preliminary analysis indicated a correlation between the type of structure and the amount of calcium excreted in the urine (Pyrah 1958, Hodgkinson and Pyrah 1958). This correlation has been confirmed in a larger series of patients, and we here consider the implications of these findings.

Methods

Selection of Patients

We included initially in this study all those patients who presented for treatment in our unit between 1954 and 1959, and who had renal or ureteric calculi composed of calcium oxalate or a mixture of calcium oxalate and calcium phosphate. Patients with vesical calculi, or calculi containing magnesium ammonium phosphate or uric acid, were excluded. Also excluded were patients with chronic renal infection or bilateral

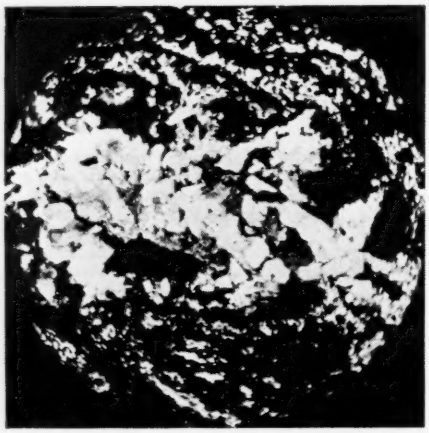

Fig. 1—Thin section of calcium-oxalate stone, crystalline type.
The large crystals in the centre of the field were of calcium oxalate dihydrate (weddellite), which had undergone recrystallisation into much smaller crystals of calcium oxalate monohydrate. Surrounding this are alternate layers of apatite and calcium-oxalate crystals.

renal impairment (urea-clearance less than half the average normal). Three children, aged 5 to 15, were also excluded.

Stone Structure

To study the crystalline structures found in urinary calculi several methods have been employed (Prien and Frondel 1947, Carr 1953), but the most powerful are those in which a thin cross-section of the stone is examined under polarised light (Ord and Shattock 1895, Randall 1942, Brandenberger et al. 1947, Lucas et al. 1950). We have used this technique to

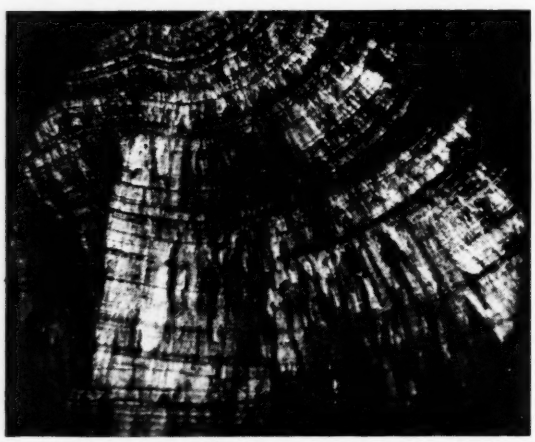

Fig. 2—Thin section of striated stone showing long needle-shaped crystals of calcium oxalate monohydrate, perpendicular to a system of microscopically thin laminations.
The photograph was taken with the slide between crossed polaroids (×24).

determine the crystalline structure of 208 oxalate-containing calculi. The composition of the calculi was also determined by X-ray diffraction, using either a Debye-Scherrer camera (Bunn 1946) or a Brindley camera (Brindley 1955).

Urine-calcium

This was determined in 158 cases by the method of Shohl and Pedley (1922), calcium excretion being expressed as the mean of three 24-hour collections, with the patient on a normal diet. The rationale of using a normal hospital diet as distinct from a low-calcium diet has already been discussed (Hodgkinson and Pyrah 1958).

Results

Structure of Oxalate-containing Calculi

Using the technique of thin sections, it is possible to distinguish two main types of structure:

"*Crystalline.*"—This type of stone is characterised by well-formed crystals of calcium oxalate monohydrate or dihydrate, arranged in disordered aggregates whose interstices are occupied by calcium phosphate (apatite) or colloidal material, or both. Individual crystals may be 1 mm. or more in size. Layers of 100 μ or more in thickness are frequent, and these are often separated by layers of apatite (fig. 1). In this type of stone the crystal outlines seem to have determined

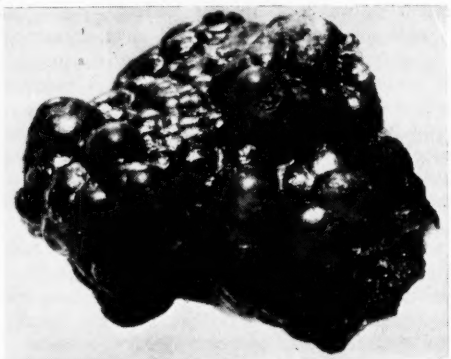

Fig. 3—To show the nodular surface of a striated type of calcium-oxalate stone.

the way in which the stone has grown, any colloidal material which is present apparently playing a secondary role.

"*Striated.*"—This type is characterised by radial striations which can often be seen with the naked eye on the fractured surface, as well as microscopically in the thin section. The striations are due to orientation of long needle-shaped crystals of calcium oxalate monohydrate perpendicular to a system of microscopically thin laminations (fig. 2). This stone usually has a blistered or nodular surface (fig. 3). Its structure seems to have been determined by the organic colloid, and distinct crystal forms are absent.

In our series 93 calculi (45%) were of the crystalline type and 29 (14%) were of the striated type. The other 86 calculi were part crystalline and part striated; in 42 of these it was possible to distinguish a crystalline or striated centre surrounded by a well-defined outer layer of contrasting structure, but in 44 there was a random distribution of crystalline and striated areas throughout the stones, and no classification was attempted.

Calcium Excretion and Stone Structure

We have defined hypercalciuria as a daily excretion of calcium in excess of 250 mg. per day by adult women, and 300 mg. per day by adult men, the subjects being on a normal diet (Hodgkinson and Pyrah 1958). Using these criteria, hypercalciuria occurred in 43% of patients with oxalate-containing stones, compared with 8% of healthy subjects (table I).

In relation to stone structure hypercalciuria was most common in patients with wholly crystalline stones, or

TABLE I—INCIDENCE OF HYPERCALCIURIA IN NORMAL ADULTS AND IN PATIENTS WITH OXALATE-CONTAINING STONES

Subjects	No. of cases	No. of cases omitting those with poor renal function	Proportion with hypercalciuria (%)
Normal adults	258	258	8
Patients with calcium-oxalate stones	50	47	34
Patients with mixed oxalate-phosphate stones	58	50	54

TABLE II—INCIDENCE OF HYPERCALCIURIA IN PATIENTS WITH "CRYSTALLINE" AND "STRIATED" CALCULI

Calculi	No. of cases	No. of cases in which urine was analysed	Proportion with hypercalciuria (%)
Crystalline throughout	93 (45%)	72	53
Striated throughout	29 (14%)	20	15
Crystalline centre, striated exterior	21 (10%)	13	15
Striated centre, crystalline exterior	21 (10%)	18	33
Mixed (not classified)	44 (21%)	35	40
Total	208	158	..

stones with a crystalline exterior (table II). The incidence of hypercalciuria in the unclassified group (40%) corresponded closely to that observed among all the patients with oxalate-containing stones (43%).

As hypercalciuria is more frequent in patients with mixed calcium-oxalate and calcium-phosphate stones, and also in those with crystalline stones, we also determined the frequency of hypercalciuria among patients with mixed oxalate-phosphate stones of crystalline structure. In 69 the calculi were of this type, and hypercalciuria was found in 52% of this group.

Discussion

The majority of stones were uniformly crystalline or striated throughout, suggesting that the environment had remained relatively constant throughout the period of stone growth. In 20% of the stones, however, there was a clearly distinguishable crystalline or striated centre with an outer layer of contrasting structure, suggesting that the environment had changed during the period of growth. In these cases one would expect that any correlation between stone structure and urine composition when the stone was removed would be related to the outer rather than the inner layers of the stone; and this is supported by our findings. In the unclassified group, which constitutes 21% of the stones analysed, there seems to be a near-equal balance of factors leading to the formation of crystalline and striated structures; and one would expect the incidence of hypercalciuria to correspond to that among all the patients with stone as a whole. This was found to be so.

The relatively high prevalence of hypercalciuria in patients with crystalline stones supports the impression gained from structural studies that many such stones are formed by the crystallisation of calcium salts from a supersaturated solution. Not all patients with crystalline stones have hypercalciuria, however, and other factors are evidently involved in the formation of these stones. In a few patients with oxalate-containing stones (Hodgkinson 1958) increased excretion of oxalic acid may be an ætiological factor, but in many there is no detectable abnormality in the composition of the urine.

The low prevalence of hypercalciuria in patients with striated stones could be taken as evidence that these stones are not usually formed by crystallisation. 5 patients with striated stones had hypercalciuria, however, and another patient was found to have primary hyperoxaluria (Pyrah, Anderson, Hodgkinson, and Zarembski 1959), a condition in which the crystalline type of stone might be expected to occur. But the last patient excreted only small amounts of calcium (30–50 mg. per day), and this may account for the absence of a crystalline structure, because there is now evidence that stone formation is influenced not only by the ionic concentration product but also by the concentrations of the individual ions in the urine. This point is well illustrated by the effect in man of aluminium-hydroxide gel, given by mouth, in reducing the intestinal absorption and urinary excretion of phosphate, and hence the rate of formation of some calcium-phosphate stones (Shorr 1945, Pyrah et al. 1956).

The rate of stone growth is reduced although reduction in phosphate excretion is accompanied by a striking increase in calcium excretion (Pyrah et al. 1956). In the rat the dietary ratio of calcium to phosphate has an important influence on the formation of calcium-phosphate stones (Gill et al. 1959, Vermeulen 1959, Vermeulen et al. 1959). These workers found that stone formation was inhibited by feeding large amounts of sodium phosphate or calcium lactate. Sodium phosphate resulted in a high urinary excretion of phosphate and a reduced excretion of calcium, whereas calcium lactate caused the opposite. Such observations may also apply in the case of oxalate ions.

Many calculi, differing widely in composition, are marked on their fractured surface by radial striations, and this is often associated with nodularity of the external surface (Schade 1923, Prien and Frondel 1947). Such markings are usually seen in areas composed of calcium oxalate monohydrate, uric acid, or calcium hydrogen phosphate dihydrate, and various attempts have been made to interpret their significance (Schade 1923, Lichtwitz 1944, Carr 1953, 1956).

Carr (1953) suggested that calculi with radial orientation are crystallised direct from solution, the organic matrix serving only to prevent disturbances in the process of crystallisation. He considered that, in such calculi, coherence depends on crystalline continuity rather than on the presence of an organic matrix; such stones he described as "concretionary". In the case of crystalline stones, he suggested that crystallisation is the result of supersaturation with respect to calcium phosphate; and that this is followed, while the crystals are still microscopic, by adsorption of organic polysaccharide material. Such stones were described as "sedimentary" (Carr 1956).

From chemical, histochemical, and microscopic studies much evidence has now accumulated that wherever there is calcification in bone or pathological tissues, including urinary calculi, organic material is always present (Howard 1951, 1954, Baker and Sison 1954, Grimes 1957, Boyce and King 1959). Our studies confirm that organic material is invariably present in urinary calculi, but whether this plays an active or a passive role in any particular case is still uncertain. At present we incline to the view that the organic matrix is active in the initiation and subsequent growth of most oxalate-containing calculi, including the crystalline type described here. The composition, structure, and rate of formation of any particular calculus will largely depend, however, on the urinary composition in that individual.

The factors which lead to the formation of a calcifiable matrix are probably numerous, and hypercalciuria itself may be one such factor. For example, we have observed an increased incidence of microscopic renal calcification in patients with hypercalciuria (Anderson, Hodgkinson, and Pyrah 1961). Such calcification seems to be preceded by changes in the mucopolysaccharide fraction of the renal ground substance (Baker and Sison 1954, Grimes 1957). Moreover, there is now indirect evidence that these calcific deposits are the precursors of many calcium-containing stones (Carr 1954, Engfeldt and Lagergren, 1958).

Summary

The majority of oxalate-containing calculi can be divided into two groups, depending on their gross and microscopic structure—namely, a "crystalline" type from patients in whom hypercalciuria is relatively common, and a "striated" type from patients in whom hypercalciuria is infrequent.

It is suggested that striated stones are formed primarily by adsorption of calcium salts on the surface of an organic matrix; whereas crystalline stones are formed primarily by crystallisation of calcium salts from a supersaturated solution, the organic matrix being of secondary importance.

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RENAL CALCIFICATION, CALCULUS FORMATION, AND THE URINARY EXCRETION OF CALCIUM

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MANY calcium-containing renal calculi originate as microscopic calcific deposits within the renal parenchyma, and in this paper we consider the urinary excretion of calcium as a possible factor in the formation of these deposits.

Engel (1951, 1952) observed that radiographic renal calcification (nephrocalcinosis) is commonly associated with stone formation, and Hellström (1955) suggested that stone formation is a consequence of the nephrocalcinosis. Renal calcification, however, is relatively rarely shown on radiographs. Mortensen et al. (1953) observed 7 cases (0·5%) among 1418 consecutive patients with radiographic evidence of nephrolithiasis, and we have observed 24 cases (1·7%) in our series of 1400 patients with renal stone (Pyrah and Hodgkinson 1960).

Here we are concerned with the more common microscopic calcification, which is not demonstrable radiographically. The finding of such deposits varies considerably, and appears to depend on the size of the deposit examined, the techniques used to prepare and examine the sections, and the number of sections examined.

Beer (1904), in a study of 100 kidneys removed at necropsy, found calcium deposits in 53%; and Stout et al. (1935) observed them in 54%. Anderson (1940), in examining 1500 apparently normal kidneys removed at necropsy, found microscopic calcium deposits in routine sections in 180 (12%). But in most cases only one section was studied, and Anderson thought that the incidence would probably have been greater if more sections had been cut.

Calcific deposits have been found in all parts of the human kidney, but most interest has centred on their occurrence within or on the surface of the renal papilla. Among 609 necropsies Randall et al. (1937) observed calcium-plaque formation in the renal papilla in 140 (23%), and these findings have been confirmed by Rosenow (1940) and Vermooten (1942). Anderson and McDonald (1946), however, in examining 168 pathological and grossly normal kidneys, found microscopic calculi in the pyramids of them all. In half of these cases the deposits were found in the first section studied, but up to ten sections were required in some cases. We have observed occasional sparse and scattered calcific deposits only in the renal pyramids of the normal non-stone-bearing kidney; in the stone-bearing kidney the deposits were far more numerous and much closer together (Pyrah 1958).

Randall (1937) showed that some calculi at least originate as calcific deposits within the parenchyma of the renal papilla after the eruption of these deposits to the surface of the papilla. Further indirect evidence that microscopic calcific deposits (not necessarily originating in the papilla) form the nidus of many stones has been provided by Carr (1954) and by Engfeldt and Lagergren (1958), who found that the composition of these deposits closely resembled that of the common calcium-containing stone.

The factors responsible for pathological calcification in the kidney have been discussed exhaustively by Barr (1932) and by Goldstein and Abeshouse (1938a and b). Howard (1951) suggested that one or both of the following conditions must exist to produce ectopic calcification: (1) a local stimulus to lay down a calcifiable matrix, and (2) an increased concentration of calcium in the extracellular fluid. Similar views have been expressed by Stout et al. (1955) in a study of renal calcification in 147 routine necropsies.

Hypercalcæmia often leads to abnormal calcification, but this happens in only a minority of patients with nephrocalcinosis or nephrolithiasis. Hypercalciuria, however, is commonly found in nephrolithiasis, and we therefore decided to compare the degree of microscopic renal calcification with the urinary excretion of calcium in a series of stone-forming patients.

Methods

Selection of Patients

We included in our survey 139 patients with renal calculus who had had a partial or total nephrectomy performed in this department between 1945 and 1959. Patients with much impairment of renal function (urea-clearance less than half the average normal), and children under 15 were excluded.

Histological Technique

The material was fixed in neutral formol-saline, and blocks of tissue were taken to show cortex, medulla, and pyramids. Slides were stained with hæmatoxylin and eosin, and by von Kossa's technique (Cameron 1930).

More than half the kidney specimens had been examined initially by other pathologists, and therefore fewer blocks of suitable kidney tissue were available for study than is desirable in such a survey. Ideally 6–8 blocks were taken from a partial nephrectomy and 8–12 blocks from a nephrectomy. Because

RELATION BETWEEN RENAL CALCIFICATION AND URINARY EXCRETION OF CALCIUM

Microscopic renal calcification	No. of cases	No. of cases with hypercalciuria
Nil	86	10 (*12%*)
Scattered	44	14 (*32%*)
Extensive	9	4 (*44%*)
Total	139	28 (*20%*)

the incidence of calcification is not uniform throughout the renal parenchyma, the greater the volume of kidney tissue sampled the more likely is calcification to be found.

If calcification was not seen in the first sections then step sections were taken through the blocks; up to three hundred slides were examined in some cases. The later examination of multiple sections from the same blocks did not materially alter the impression derived from the first sections, and in no case was extensive calcification observed in the step sections which was not also apparent in the first sections.

Tubular calcification was recorded as "scattered" and "extensive". Calcification in cysts, whether large or small, and small dense deposits in the cortex or medulla devoid of tubular pattern were not recorded.

Biochemical Methods

Urine-calcium was determined by the method of Shohl and Pedley (1922), calcium excretion being expressed as the mean of three 24-hour collections, with the patient on a normal diet. Measurements were made before operation in most cases, or at least a week after operation.

Urine-oxalic-acid was determined by a modification of the method of Powers and Levatin (Hodgkinson and Zarembski, 1961).

Results

Microscopic calcification was observed in 53 of our present series (38%). This is less than was observed previously in a smaller series (Pyrah 1958), and the difference seems to be due partly to the selection of cases. A further cause of discrepancy lies in the selection of the piece of kidney to be studied, for we have observed that the degree of calcification varies widely between closely adjacent portions of the kidney (Holdsworth and Anderson, to be published).

We have defined hypercalciuria as a daily urinary excretion of calcium in excess of 250 mg. per day by adult women, and 300 mg. per day by adult men, with the subjects on a normal diet (Hodgkinson and Pyrah 1958); and in 1958 we found that the incidence of hypercalciuria in healthy non-stone-bearing adults was 8%. Using these criteria 16% of patients with no evidence of microscopic calcification had hypercalciuria, compared with 22% of patients with scattered microscopic calcification and 44% with more extensive calcification (see table).

In all, 53 cases showed renal calcification, and of these 18 had hypercalciuria. If the prevalence of hypercalciuria had been the same in this group as in the group showing no calcification (12%), only 6 cases might have been expected to have hypercalciuria, whereas the actual incidence was three times this number.

Discussion

The frequency of hypercalciuria in the series as a whole (20%) is lower than we found in an unselected series of patients with calcium-containing renal stone (Hodgkinson and Pyrah 1958), and this difference is attributable to selection.

Although some correlation is demonstrable between hypercalciuria and the degree of renal calcification (see table), we conclude that hypercalciuria is not the principal factor determining the formation of these deposits. This is apparent from the fact that hypercalciuria was absent in 35 patients with unequivocal renal calcification. Moreover, 10 of the 28 patients with hypercalciuria had no evidence of renal calcification. More extensive serial sectioning would probably have revealed occasional calcific deposits in these 10 cases, but this would not affect the conclusions which we have drawn from this study.

The relation between hypercalciuria and renal calcification resembles that between hypercalciuria and the formation of calcium-containing renal stones. In the latter, hypercalciuria is observed in 30–50% of cases, depending on the type of stone, but hypercalciuria is not always associated with stone (Hodgkinson and Pyrah 1958).

Hypercalcæmia, another possible contributory factor in renal calcification, was observed unequivocally in only 2 cases in the series. In one of these the hypercalcæmia was due to a parathyroid adenoma which was removed surgically. Primary hyperparathyroidism is strongly suspected in the second case, but an operation has not yet been performed. In the other cases the serum-calcium level was within the normal range (9·0–10·7 mg. per 100 ml.) on repeated testing.

Most of the renal deposits appeared to consist entirely of calcium phosphate, but calcium oxalate deposits were observed in 2 patients. One of these had an excessive urinary excretion of oxalic acid on a normal diet (primary hyperoxaluria), but in the second the excretion of oxalic acid was within normal limits, and the calcium-oxalate deposits remain unexplained. The urinary excretion of oxalic acid was measured in a further 15 cases in this series, but in all of them it was normal or only slightly raised.

From the available evidence it seems that an increased concentration of calcium or oxalate ions in the extracellular fluid or urine favours the deposition of calcium in the renal parenchyma, but these abnormalities are seen in only a minority. In the majority of cases of microscopic renal calcification one has to consider a local stimulus to calcification, as suggested by Howard (1951), and this aspect will later be considered in greater detail (Holdsworth and Hodgkinson 1961).

Summary

Hypercalciuria has been considered as a possible factor in the formation of microscopic calcific deposits within the renal parenchyma.

From observations on patients with calcium-containing renal stones, hypercalciuria seems to be a contributory factor in the formation of these deposits, but other important factors are also involved. Attention is drawn to the similarity between this relationship and that which exists between hypercalciuria and the calcium-containing renal stone.

Other possible contributory factors, in particular hypercalcæmia and hyperoxaluria, have been examined in relation to renal calcification and calculus formation.

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PRECIPITATING AUTOANTIBODIES IN SJÖGREN'S DISEASE

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AMONG the various diseases which have been shown, or claimed, to be associated with autoimmunisation, two examples may be used to illustrate conditions in which the immunological responses appear to be of a fundamentally different nature:

First, Hashimoto's disease, a condition consisting essentially of a destructive inflammatory lesion of a single organ, which is accompanied by the development of autoantibodies reacting specifically with normal constituents of that organ.

Secondly, systemic lupus erythematosus (S.L.E.), a disease with lesions involving many organs and tissues, which is accompanied by the development of autoantibodies reacting with cellular constituents—e.g., nuclear material—common to a wide variety of tissues.

Sjögren's disease (used here to denote keratoconjunctivitis sicca with or without the commonly associated manifestations) is of interest in having features in common with both the above conditions. In a study of twenty-eight cases, Heaton (1959) emphasised its similarities to S.L.E. In ten of these, the L.E.-cell test was positive, and many of the patients presented features and laboratory findings commonly observed in S.L.E. The similarity of Sjögren's disease to Hashimoto's disease rests mainly upon the similar histological changes observed in the lacrimal glands, and sometimes in the salivary glands, in the former, and in the thyroid in the latter (Cardell and Gurling 1954). Other points of similarity were described by Jones (1958), who examined the serum of forty patients with Sjögren's disease for antibodies reacting with tissue extracts, and detected a factor which reacted to give a precipitate with extracts of salivary and lacrimal glands. There was some doubt about the organ-specificity of this reaction, for the serum reacted also with kidney extracts.

In this paper we describe the results of a search for precipitating antibodies, reacting with extracts of tissues, in the serum of patients with Sjögren's disease. Two distinct precipitating autoantibodies have been demonstrated, both of which react with intracellular antigens present in a wide variety of tissues.

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Materials and Methods

Serum was obtained from hospital patients and stored at −20°C before testing. The diagnosis of Sjögren's disease was made from the case-history and clinical condition, supported by positive Schirmer and rose-bengal tests. Control serum was obtained from patients without clinical evidence of Sjögren's disease, Mikulicz's disease, or the collagen diseases. Most of the control specimens were obtained primarily for blood-grouping, and the patients were thus a selected group in that they were candidates for blood-transfusion.

Tissue extracts were prepared from human tissues obtained within a few hours of death, from thyroid tissue removed surgically from patients with thyrotoxicosis or simple non-toxic goitre, and from animal tissues taken immediately after death. Extracts were prepared from fresh or frozen stored tissues as follows:

The tissue was sieved or finely sliced and suspended in an equal volume of 0·9% NaCl solution containing a quarter volume of isotonic phosphate buffer at pH 7·5. The suspension was treated in an M.S.E. homogeniser at top speed for 3 minutes, and the homogenate was centrifuged at 3800 r.p.m. for 30 minutes. The supernate was stored at −20°C and used undiluted as tissue extract. The extraction procedure was carried out at 0–5°C.

Tissue extracts and serum used for quantitative precipitin experiments and for the preparation of precipitate for analysis were previously centrifuged twice at 35,000*g* for 30 minutes to remove finer particles which might otherwise be regarded as a part of the specific precipitates.

Precipitin tests in agar were performed by an Ouchterlony technique, using 9 cm. diameter petri dishes, each containing 20 ml. of 1·7% Difco 'Bacto' agar in a solution of 0·9% NaCl and 0·1% sodium azide. The sizes of the wells and their distances apart were varied in different experiments. For detection of precipitins, the serum and antigen (tissue extract) wells were of 10 mm. diameter, and their centres were 15 mm. apart. Each serum was tested undiluted, and diluted 1 in 8 with 0·9% NaCl. The test plates were kept at room temperature and examined daily for 10 days. Positive serum specimens were titrated in twofold or fourfold dilutions.

Thyroid antibody was detected by Boyden's hæmagglutination method, using red cells treated with tannic acid and coated with "purified" thyroglobulin, as described by Roitt and Doniach (1958).

Investigations and Results

Serum from twenty-nine patients with Sjögren's disease and a hundred and fifty control specimens were tested for precipitins. In view of Jones's (1958) results, lacrimal and salivary-gland extracts were used at first as antigens, but it soon became clear that extracts of various other organs were equally effective, and although all serum specimens were tested with extracts of thyroid, salivary gland, and spleen, thyroid-tissue extracts were used as antigens in most of the later investigations.

A positive result was recorded when one or more thin straight sharply defined lines of white precipitate developed, within 3 days, between and at right angles to the axis of the serum and extract wells (fig. 1). One of the difficulties encountered was the development of a zone of opacity (halo) in the agar around the tissue-extract wells. When dense, this tended to obscure the result. This difficulty was largely overcome by using thyroid-tissue extract, which gave a less dense halo than extracts of most other tissues. When tested undiluted, some of the more strongly reacting specimens gave precipitates which were difficult to detect because they were very close to the tissue-extract wells. At a dilution of 1 in 8, however, such sera gave conspicuous precipitates at some distance from the tissue-extract wells.

Positive tests were observed with nine specimens of Sjögren serum and with two control specimens. One of the

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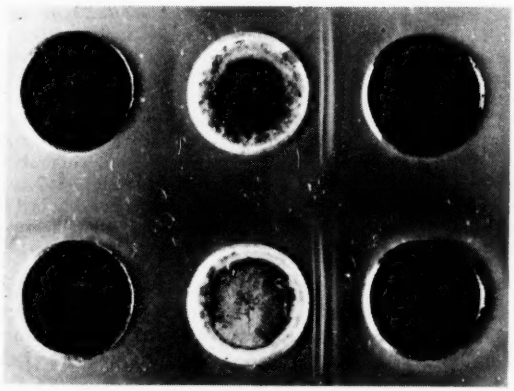

Fig. 1—Precipitin tests.
A positive serum (right wells) and a negative serum (left wells), both undiluted (lower) and 1 in 8 (upper). The central wells contained thyroid-tissue extract. The positive serum (*Scr*) gives two lines of precipitate at 1 in 8 dilution, and three lines undiluted.

controls was from a patient thought to have a parotid tumour who was later shown by parotid biopsy to have Mikulicz's disease. The other positive control serum was from a patient with aplastic anæmia who had had repeated blood-transfusions and who showed no evidence of Sjögren's disease or the collagen diseases. The precipitating titres of the nine positive Sjögren specimens are given in table I. In these titrations, some of the more strongly reacting serum specimens gave two parallel lines of precipitate at some of the dilutions, and more complex

TABLE I—PRECIPITATING AND COMPLEMENT-FIXING ANTIBODY TITRES OF SJÖGREN SERUM

Serum	Precipitating titre	Complement-fixing titre with extracts of	
		Thyroid	Kidney
*Tra**	256	512	1024
*Don**	64	nil	nil
*Ral**	256	1024	1024
*Plu**	64	256	256
*Scr**	256	64	256
*Kie**	4	<4	<4
Har	4	<4	<4
Wal	4	<4	<4
War	4	4	16
20 specimens	nil	<4	<4

* Identities of the precipitins in these specimens are given in table II.

appearances with three lines of precipitate sometimes developed. Control negative serum was also tested in doubling dilutions, and it occasionally gave a single faint short line of precipitate. This finding was inconstant, was observed usually only at serum dilutions 1 in 16 and 1 in 32, and took 5 days or more to appear. By contrast, the Sjögren precipitates were reproducible, they occurred with all serum dilutions up to titre, they appeared within 3 days, and they were denser, more sharply defined, and much longer. Heating the Sjögren sera at 56°C for 30 minutes had no effect on the precipitating factors, but these were progressively weakened at higher temperatures. The Sjögren precipitates resisted washing of the agar in saline and water, followed by drying, and they were stained by amido-black.

Immunoelectrophoresis in agar was performed upon four of the more strongly reacting Sjögren specimens (*Tra*, *Don*, *Plu*, and *Ral*) using a technique closely similar to that described by Goudie (1960). The precipitating factors in all four had the electrophoretic mobility and pattern of γ-globulin. From these results, and from experiments described below, involving the annulment of the precipitating factors of tissue extracts, we concluded that the serum factors concerned are antibodies.

Comparison of the precipitating sera, to determine whether they contained the same or different antibodies, was carried out by two methods:

The first consisted of Ouchterlony tests, in which the serum specimens to be compared were placed in closely adjacent wells, and reacted with antigens diffusing from a single well containing tissue extract. The precipitates formed could usually be seen to fuse completely, to fuse partially with " spur " formation, or to behave independently and cross—suggesting respectively complete identity, partial identity, or non-identity of the antibodies concerned (Ouchterlony 1953). Such tests are known to have certain limitations (Wilson and Pringle 1956), and in particular they are not ideally suited for investigations on serum containing more than one precipitating antibody. Nevertheless, with suitable serum dilutions, and the arrangement of wells shown in fig. 2, they provided useful information. Thus two specimens—*Tra* and *Don*—gave precipitates which crossed, and which appeared to contain different antibodies (for convenience these have been termed anti-SjT and anti-SjD respectively). Serum *Ral* gave two lines of precipitate, one of which fused with the serum *Tra* line and the other with the serum *Don* line: serum *Ral* thus appeared to contain both antibodies. Serum *Plu*, which sometimes gave a single rather thick line and sometimes two lines close together, also appeared to contain both antibodies; while serum *Scr* contained, in addition, a third antibody. With four of the positive Sjögren's sera, the reactions were too weak for this technique.

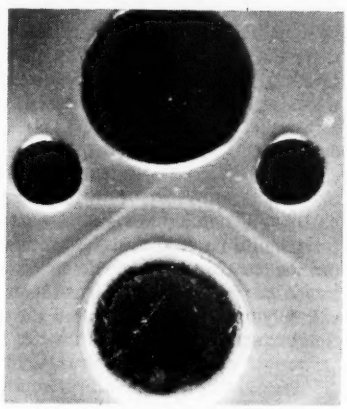

Fig. 2—Comparison of antibodies.
The lower large well contains thyroid-tissue extract, and the upper 3 wells contain dilutions of three positive serum specimens. The serum in the left small well gives a reaction of non-identity, and that in the right small well a reaction of identity, with the serum in the upper large well.

In the second method of comparing the reactions of the positive specimens, tissue extracts were treated overnight at 4°C with enough precipitating serum to annul the corresponding antigen. The treated extract was tested by the Ouchterlony technique with the same serum (to confirm annulment), and with other positive sera. Control tests were set up with the extract treated with normal serum. The results, examples of which are shown in table II, confirm the conclusions drawn

TABLE II—PRECIPITIN TESTS WITH TISSUE EXTRACT TREATED WITH SJÖGREN SERUM

Tissue extract treated with serum of †	Treated tissue extract tested with serum of †						Identity of precipitins
	Tra	*Don*	*Ral*	*Plu*	*Scr*	Normal serum	
Tra	−	+	+	+	+	−	Anti-SjT
Don	+	−	+	+	+	−	Anti-SjD
Tra+*Don* ..	−	−	−	−	+	−	Anti-SjT+anti-SjD
Ral	−	−	−	−	+	−	Anti-SjT+anti-SjD
Plu	−	−	−	−	+	−	Anti-SjT+anti-SjD
Scr	−	−	−	−	−	−	Anti-SjT+anti-SjD +anti-? †
Kie	+	−	+	+	+	−	Anti-SjD
Normal serum	+	+	+	+	+	−	Nil

† Serum *Scr* contains a third precipitating factor.

from the comparison of the antibodies by direct tests. Three of the specimens (*Wal*, *Har*, and *War*) were too weak to annul the corresponding antigens without diluting them excessively, and the precipitating factors in these specimens were not identified. Nor was it possible to identify the precipitating factors in the two positive controls—in one case because the reaction was too weak, and in the other because insufficient serum was available.

Two of the patients with Sjögren's disease also had thyroid enlargement. One of these (*War*) proved to have Hashimoto's disease, while the diagnosis of the other (*Har*) remains uncertain. The serum of these two patients contained precipitating antibody to thyroglobulin, demonstrable by the Ouchterlony method, using as antigen purified thyroglobulin prepared by the method of Derrien et al. (1948). The presence of precipitating factors other than antithyroglobulin in these two sera was demonstrated by Ouchterlony tests with extracts of tissues other than thyroid. None of the other Sjögren specimens reacted to give a precipitate with thyroglobulin, but of twenty-four which were tested by the more sensitive hæmagglutination technique, ten were positive and of these four had titres of over 1000. The positive specimens included five which contained Sjögren-type precipitating factors (*Tra*, *Don*, *Scr*, *War*, and *Har*). Control specimens from sixty-five patients of similar age and sex were also tested by the hæmagglutination technique: nine were positive, and only one had a titre of over 1000. Thus there is clearly an increased incidence of thyroid antibody, reacting presumably with thyroglobulin, in the group of patients with Sjögren's disease.

Incidence of the Antigens

1. *In individuals.*—Eighty thyroid-gland extracts, stored at −20°C for up to 2 years, all reacted with serum *Tra* (anti-SjT). Antigen SjD was found to deteriorate in stored extracts; accordingly tissues taken post mortem from forty subjects were extracted, and the extracts were tested immediately with serum *Don* (anti-SjD). SjD was demonstrated in extracts of the tissues of all forty, although some extracts gave a positive result only after concentration by freeze-drying and reconstitution to a smaller volume. It seems likely that both antigens are regularly present in human tissues.

2. *In various tissues.*—Tests with serum *Tra* and serum *Don* revealed both antigens in extracts of thyroid, salivary and lacrimal glands, spleen, kidney, testis, liver, adrenal, and brain. SjT was detected without difficulty in all of these tissues, but tests with anti-SjD often gave weak or doubtful results, particularly with tissue extracts producing a dense halo—e.g., liver, adrenal, and brain—of which only occasional extracts gave conclusive reactions with this serum. The precipitating titres of tissue extracts was low for both types of antibody serum, being usually 1 in 4 or less, and rarely 1 in 8. Extracts of tissues of low cellularity—e.g., cartilage, fascia, and umbilical cord, and also tears, joint fluid, mucinous ovarian-cyst fluid, whole blood, serum, and extracts of red cells—gave negative results with both specimens. Leucocytes were obtained by the method of Walford (1960) and extracted with an equal volume of saline by freezing and thawing, and shaking mechanically. Extracts were thus prepared from four cases of chronic lymphatic leukæmia and from three cases of chronic myeloid leukæmia. The lymphatic leucocytic extracts contained both SjT and SjD antigens: the myeloid leucocytic extracts contained neither, and it was later shown that incubation of a mixture of equal volumes of myeloid leucocytic extract and thyroid gland extract for 3 hours at 37°C resulted in loss of both the antigens. The myeloid leucocytic extracts thus contain one or more inhibitory substances, possibly of enzymic nature. Extracts of leucocytes of normal blood were similarly inhibitory. Complete fusion of precipitates was observed in Ouchterlony tests in which various tissue extracts, including lymphatic leucocytic extracts, placed in pairs in closely adjacent wells, reacted with antibody diffusing from a single serum well. This result was obtained with both anti-SjT and anti-SjD serum, and suggests that different tissues contain identical antigens. The results with lymphatic leucocytic extracts indicate that both the antigens are cellular constituents.

3. *In animal tissues.*—Extracts of liver, kidney, and spleen, prepared from rabbits, mice, guineapigs, and rats, were tested for the antigens. SjT was demonstrated in the tissues of rabbits, mice, and guineapigs, but not in rat tissues, while SjD was detected only in guineapig tissues. The methods described in the previous paragraph showed reactions of identity between the human and animal antigens.

The Autoimmune Nature of the Antibodies

During this investigation, precipitin tests were performed upon the serum of a group of patients with various collagen diseases, and these specimens were found to be a fruitful source not only of anti-SjT and anti-SjD but also of other precipitating antibodies. One serum specimen, from a patient with rheumatoid arthritis, contained anti-SjT and anti-SjD, both in low titre. When the patient died, both the antigens were detected in an extract of the spleen. This result indicates the autoimmune nature of the antibodies.

Features of the Antigens

(*a*) *The effect of heat* was investigated by testing tissue extracts heated at various temperatures for an hour. SjT was weakened at 45°C, and destroyed at 55°C. SjD withstood 55°C, and was destroyed at 65°C.

(*b*) *Effect of enzymes.*—Thyroid tissue extract, buffered at pH 7·4, was treated with 0·4% trypsin (British Drug Houses). This treatment destroyed the antigen SjT, but SjD was not obviously affected: antigen SjT was also destroyed by incubation with crystalline chymotrypsin or papain. Treatment with deoxyribonuclease and ribonuclease, under conditions suitable for enzymic activity, was without effect on either of the antigens.

(*c*) *Tests with nuclear constituents.*—In view of the demonstration by Seligmann (1958) and Deicher et al. (1959) of precipitating and complement-fixing antibodies to deoxyribonucleoprotein and deoxyribonucleic acid (D.N.A.) in the serum of patients with S.L.E., deoxyribonucleoprotein, D.N.A., and histone were prepared from human spleen and thyroid by the method of Mirsky and Pollister (1946). None of the preparations, tested over a wide range of dilutions, reacted in Ouchterlony tests, nor in Oudin-tube precipitin tests in 0·5% agar. These preparations were without annulling effect upon anti-SjT and anti-SjD serum. Precipitation reactions were demonstrated with the deoxyribonucleoprotein and D.N.A. preparations with the serum of a patient with active S.L.E.

Complement-fixation tests were performed, using doubling dilutions of Sjögren serum, and various tissue extracts as antigens:

The technique used was that described elsewhere (Anderson et al. 1959). Complement-fixation was demonstrated with some of the precipitating serum specimens, and was non-organ-specific. The results with thyroid and kidney extracts, shown in table I, suggest that complement is fixed by the reaction of anti-SjT, but not by that of anti-SjD.

Fluorescent antibody studies were performed by the " sandwich " technique, using unfixed frozen sections of the livers of laboratory animals, and rabbit antihuman-globulin serum labelled with fluorescein. This study is incomplete, and the reactions are clearly very complex:

With Sjögren serum, three types of fluorescence have been observed—diffuse cytoplasmic, homogeneous nuclear, and speckled nuclear (Beck 1961). None of these effects was confined to serum containing precipitins, but such specimens had, in general, much higher titres than the non-precipitating Sjögren serum. Specimens containing anti-SjT invariably gave speckled nuclear and diffuse-cytoplasmic fluorescence, but for

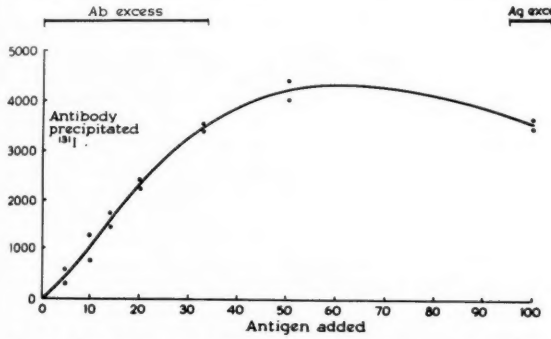

Fig. 3—Quantitative precipitin curve with ^{131}I-labelled serum Tra (anti-SjT) and thyroid-tissue extract; serum dilution 1 in 64.

neither of these effects were the serum titres closely parallel to their precipitating titres. Specimens containing anti-SjD gave cytoplasmic and either or both types of nuclear fluorescence, but none of the types was common to all such sera. No significant differences were observed with liver sections of different mammalian species, and it remains undecided whether any of these types of fluorescence is attributable to the precipitating antibodies of the Sjögren serum.

Further Investigations upon Antigen SjT

Attempts were made to determine the intracellular site of this antigen by testing for antigenicity fractions of homogenised tissues:

10% suspensions of human liver, spleen, and thyroid, and of rabbit liver in 0·25*M* sucrose were homogenised in a mechanical piston-type blender and the homogenates were fractioned by differential centrifugation (Hogeboom and Schneider 1955). The supernatant protein (" cell sap ") regularly annulled the anti-SjT in suitable dilutions of *Tra* serum, while the microsomal and mitochondrial fractions, extracted by freezing and thawing with an equal volume of buffered saline at pH 7·2, were invariably devoid of antigenic activity. Extracts of the nuclear fraction also were usually negative but occasionally weakly antigenic: since this fraction always contained some non-disrupted cells, the last finding has no significance. The antigen was detected in neutralised extracts of " clean " nuclear preparations containing no intact cells, prepared by disintegrating tissues in 1% citric acid. This does not indicate that the antigen is a nuclear constituent, for it was later shown that acidification of a crude tissue extract to pH 5 resulted in deposition of a heavy precipitate containing the antigen, and it may be that the antigen is a cytoplasmic constituent which is precipitated on to the nuclei in citric-acid preparations.

Quantitative precipitin curves were constructed using constant amounts of *Tra* serum (anti-SjT) and increasing concentrations of tissue extract:

As the precipitates were small, an indication of the amount of antibody precipitated was given by using *Tra* serum labelled with radioiodine (^{131}I) (Francis et al. 1954), and measuring the radioactivity of the washed precipitates. The supernates were tested for free antigen and antibody, and control tests were performed with ^{131}I-labelled normal serum.

The curve for *Tra* serum was of the classical type (fig. 3) described by Heidelberger and Kendall (1935), with no evidence of inhibition of precipitation in the zone of antibody excess.

Specific precipitates prepared by mixing *Tra* serum with tissue extracts were washed in saline and analysed for carbohydrate and nucleic acids as described by Paul (1958). Negative results were obtained.

L.E.-cell tests on the serum of all the patients with Sjögren's disease were negative.

Discussion

The aim of this investigation was to determine whether precipitating antibodies could be detected in the serum of patients with Sjögren's disease; and, if so, whether they reacted specifically with antigenic constituents of lacrimal and salivary glands. The Ouchterlony technique adopted is unusual in the large size of the wells, in their spacing, and in the concentration of tissue extract used as antigens. These details are likely to be important, and we have therefore described them fully. Jones (1958), who used a complex arrangement of wells, demonstrated precipitins in Sjögren's disease, while other workers (Deicher et al. 1960) have failed to demonstrate precipitins in Sjögren serum which reacted with tissue extracts to fix complement.

We had no difficulty in recognising the specific precipitates formed by strongly reacting serum and tissue extracts, but some of the " artefacts " obscured or simulated weak reactions, and accordingly the more strongly reacting sera and tissue extracts were used to investigate the antigen-antibody reactions.

Two distinct precipitating antibodies were demonstrated in Sjögren serum, and one serum (*Scr*) contained a third. Both the corresponding antigens were present in a wide range of cellular tissues, including animal tissues: their presence in lymphatic leukæmic leucocytic extracts indicates that they are cellular constituents. In view of the small amounts of the antigens extracted from tissues, their identification is likely to be difficult. There is good evidence that neither antigen is present in deoxyribonucleoprotein, but their intracellular site remains undetermined. One antigen, SjT, is likely to be of protein nature; it is destroyed by heating at 55°C and by proteolytic enzymes. The other, SjD, is relatively heat-stable and resistant to trypsin. The detection of both antigens in tissue extracts of all subjects tested, including the spleen extract of a patient whose serum contained both the antibodies, indicates that these are autoantibodies and not natural or immune isoantibodies. Complement-fixation reactions between serum and tissue extracts have been described by Gajdusek (1958) and by other investigators with serum from patients with S.L.E. and certain chronic diseases, and by Deicher et al. (1960) with serum from patients with Sjögren's disease. The demonstration that such reactions correspond to the presence of precipitating antibody (anti-SjT) in the serum provides opportunity for isolation and further analysis of the antigen concerned.

One of the striking features of the antibodies is their high precipitating titres in some of the sera. The precipitin reaction, even when demonstrated by the Ouchterlony technique, is a relatively insensitive test for antibody; and precipitating titres of the order demonstrated indicate the presence in the serum of large amounts of antibody. The patients' clinical condition did not suggest that the presence or titre of either antibody correlated with the severity of the eye changes, nor with the presence or absence of polyarthritis, and it therefore seems unlikely that the antibodies are of pathogenic importance. The demonstration of a precipitating factor in the serum of a patient with Mikulicz's disease is not surprising, for Morgan and Castleman (1953) and Morgan (1954) have provided good histological evidence that Sjögren's disease and Mikulicz's disease are variants of the same pathological condition.

As already stated, our interest in Sjögren's disease was aroused by its similarity to Hashimoto's disease and its association with the collagen diseases. The demonstration,

in cases of Sjögren's disease, of precipitating antibodies which react with extracts of many tissues, and of antibodies to nuclear and cytoplasmic constituents by the fluorescent-antibody technique, strengthens this association. But failure to detect organ-specific antibodies reacting with salivary or lacrimal gland extracts does not rule out the possibility of their existence; for specific antibodies not detectable by the precipitin or complement-fixation reactions could be present, or it may be that cell-bound immunity of the delayed-hypersensitivity type is responsible for the changes in Sjögren's disease. Waksman (1959) has suggested that this type of immune reaction, rather than the development of circulating antibodies, may be responsible for the pathological changes in various experimental and naturally occurring autoimmune diseases, including autoimmune thyroiditis.

In view of the similarities between Sjögren's disease and Hashimoto's disease (Jones 1958), we have looked into the occurrence of the two conditions together:

Many of the reported series of Sjögren's disease include patients with thyroid enlargement or a history of thyroidectomy (e.g., Gifford et al. 1943, Lutman and Favata 1946, Gruber 1956, Heaton 1959, Denko and Bergenstal 1960), but the reasons for thyroidectomy and the nature of the goitre are not stated in these reports. Among the cases of Gifford et al. (1943), one was said to be hypothyroid, and two had "low basal metabolism". Stoltze et al. (1960), in reviewing two hundred and forty-eight cases, state that thyroid disease was present in 20%, including toxic nodular, adenomatous, and exophthalmic goitre, thyroiditis, myxœdema, and carcinoma, but further details not supplied.

It is not clear, from these reports, whether Hashimoto's disease is found more commonly in patients with Sjögren's disease than in other patients. In our present investigation thyroid antibodies were detected by the tanned-cell hæmagglutination method in ten of twenty-four serum specimens from patients with Sjögren's disease. One of the patients also had Hashimoto's disease, and another had a goitre of undetermined nature: serum from both these patients gave a positive precipitin test for antithyroglobulin. These findings suggest an increased prevalence of various degrees of chronic thyroiditis in Sjögren's disease, and they agree with those of Bunim (1961), who found antibodies to thyroglobulin in the serum of eleven out of forty patients with Sjögren's syndrome. Five of these had thyroid enlargements, two of which were attributed to Hashimoto's disease.

We conclude from our investigation that patients with Sjögren's disease are prone to develop both thyroid-specific and non-organ-specific autoantibodies to tissue constituents. The same two classes of antibody are found in some patients with Hashimoto's disease, for White (1959), Holborow (1960), and White et al. (1961) have reported antibodies to nuclear material in a proportion of cases. An association is thus becoming increasingly evident between the organ-specific immunity of autoimmune thyroiditis and the non-organ-specific immunity of the collagen diseases. Since patients with collagen diseases, and in particular S.L.E., are especially prone to react immunologically to injection of weak antigens (Callender and Race 1946), our findings also support the conclusion of White et al. (1961) that an unduly responsive immunity mechanism is likely to be an important ætiological factor in some cases of autoimmune thyroiditis.

Summary

Precipitating autoantibodies, reacting with extracts of human and some animal tissues, were detected in the serum of nine of twenty-nine patients with Sjögren's disease. Two antigen-antibody systems are concerned, some serum specimens containing both antibodies, others either one alone. The antibodies in some specimens were of unusually high precipitating titre. The antigens are cellular constituents, present in small amounts in a wide variety of tissues and in leukæmic leucocytes: they differ in their sensitivity to trypsin and to heat. Antibodies reacting specifically with lacrimal or salivary gland extracts were not detected in any of the specimens of Sjögren serum, but ten of the specimens contained antibody to thyroglobulin. The results demonstrate an association between organ-specific and non-organ-specific autoimmune diseases.

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CONSTRICTIONS IN NORMAL HUMAN CHROMOSOMES

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IDENTIFICATION of the different pairs of human chromosomes is now based on three criteria—namely, the length of the chromosome, the position of the centromere, and the presence of satellites. Most workers agree that, given preparations of good technical quality, chromosome pairs no. 1, 2, 3, and 16, and the Y chromosome can readily be distinguished with certainty. The remaining chromosomes can only be classified into subgroups—i.e., 6–12, 13–15, 17–18, 19–20, and 21–22. The X chromosome belongs to the group 6–12, but it cannot be defined more exactly. The size of the chromosomes and the arm ratios differ too little to make further distinction between indi-

Fig. 1—(*a*) Enlarged photomicrograph of a constricted chromosome which, in this case, appears almost dicentric (×2000); (*b*) and (*c*) are further examples of the constricted chromosome (×2400 and 3350).

The constricted portions of the long arms appear very thin and the " normal " parts of the chromatids start abruptly.

vidual chromosomes within the larger subgroups anything but grossly arbitrary.

This paper deals with an obvious constriction, which makes possible the definite recognition of one of the chromosomes of the 6–12 group; and with less obvious constrictions in other chromosomes.

Observations

Only preparations made from leucocyte cultures according to the method of Moorhead et al. (1960) have been used for this investigation.

Fig. 2—Slightly schematic drawings of the same chromosomes as in fig. 1 (×2250).

I have observed a typical constriction in one of the chromosomes of the 6-12 group. A portion of each long arm, beginning from the centromere, appears thinner than the rest of the chromatid. This segment measures a third to a sixth of the length of the long arms, and it obviously contains less chromatin material than usual. It is often shaped like a satellite, as if the chromosome were composed of a chromosome 21–22 translocated on to a chromosome 13–15. The centromere, which usually appears ring-like in normal chromosomes, seems to be located exactly at the ends of the short arms. Then comes a tiny thickening of normal chromatid width. After this thickening the long arms become very thin for a short distance, and thereafter the normal chromatids start abruptly. This applies to cells in which the chromosomes

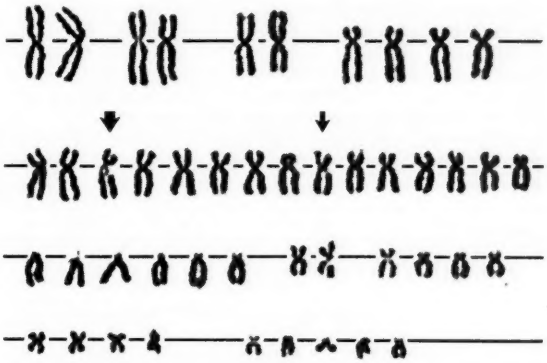

Fig. 3—Karyotype of a normal male (×2250).

The constriction in one of the biggest chromosomes of group 6–12 is marked with a large arrow. The chromosome marked with a smaller arrow also contains a constriction which is less obvious and cannot easily be distinguished in the photomicrograph. The arrangement of the chromosomes of the 6–12 group has been made by eye according to size only.

are of " normal " length and width. In very long and thin chromosomes it often seems as if the chromatids of the long arms were uniformly thin over a short distance (about a third to a quarter of their total length), starting from the centromere. In cells where the chromosomes are rather short and thick, this peculiar chromosome sometimes appears almost dicentric, with a tiny thickening about the size of a centromere between the two constrictions.

In fig. 1 examples of the constricted chromosome are seen at high magnification. Fig. 2 shows slightly schematic drawings of the same chromosomes, made by eye with the aid of the microscope. The chromosome is one of the biggest and most terminally inserted chromosomes of the 6–12 group. Inspection and rough measurements of enlarged photomicrographs and drawings place it as no. 7–9 according to size. Fig. 3 is a karyotype of a normal male; the chromosome (marked with a large arrow) is placed as a no. 7 according to size, but it could just as well have been called a 6 or an 8.

In some cells from different subjects a constriction—of the same type but smaller and much less obvious—has been seen in another, perhaps smaller, chromosome of the same group. An example of this is the chromosome marked with the small arrow in fig. 3.

Since detecting these peculiar chromosomes, I have searched systematically for them in preparations from twelve subjects previously investigated for other reasons. From each of these (some analysed before) good or excellent metaphase cells have been examined. Only cells judged as " readily analysable " have been studied. The results are presented in the table.

DISTRIBUTION OF CONSTRICTED GROUP 6–12 CHROMOSOMES

Subject no.	Clinical condition	Chromosome complement	No. of cells with one constricted chromosome 6–12	No. of cells with two constricted chromosomes 6–12	No. of cells without visible constriction of chromosomes 6–12	Total no. of cells examined
1	Normal male	2n=46, XY	28	18	12	58
2	Normal male	2n=46, XY	17	1	10	28
3	Normal male	2n=46, XY	3	3	2	8
4	Normal male	2n=46, XY	9	1	4	14
5	Normal male	2n=46, XY	14	..	1	15
6	Normal female	2n=46, XX	12	4	10	26
7	Normal female	2n=46, XX	12	1	8	21
8	Normal female	2n=46, XX	7	2	9	18
9	Klinefelter's syndrome	2n=47, XXY	11	4	5	20
10	Klinefelter's syndrome	2n=47, XXY	8	..	4	12
11	Turner's syndrome	Mosaic:				
		2n=45, XO	2	1	9	12
		2n=46, XX	3	..	14	17
12	Turner's syndrome	Mosaic:				
		2n=45, XO	6	2	6	14
		2n=46, XX	4	1	5	10
Total			136	38	99	273

There is seldom a very obvious constriction in two chromosomes of the same cell. If one is quite easy to detect, the other, if visible at all, is usually a little diffuse, and it nearly always seems to affect a smaller chromosome of the 6–12 group. Thus the constriction in two chromosomes, when detectable, is not necessarily a feature of homologous chromosomes.

Another observation has been made. In some cells from different people a very small constriction close to the centromere has been seen in one and occasionally in both chromosomes no. 1. This has been seen in about every twentieth cell examined.

Discussion and Conclusions

Cells from eight clinically and cytogenetically normal people contain one or two chromosomes 6–12 with the constriction. It seems, therefore, that this is a normal feature of the human karyotype.

Patau (1961), in a recent paper, briefly mentions having seen an inconstant secondary constriction in an autosome of the group 6–12.

In my opinion, failure to demonstrate the constriction in many cells is due mainly to technical difficulties, for one must remember that the dimensions of the constriction are close to the limits of the resolving capacity of the light microscope.

It is possible that the constriction may be a feature of one of the X chromosomes (or occasionally of both). Ohno and Makino (1961) and Stewart and Sanderson (1961) have presented evidence in favour of the hypothesis that sex chromatin is derived from a single X chromosome. Thus, if the two X chromosomes are morphologically different in metaphase cells also, it is not unlikely that one of them might have the constriction described. Unfortunately, I have not had an opportunity to study triple-X females.

Many facts weigh against the hypothesis of the clearly constricted chromosome being an X. It is found equally often in males and in females, and it occurs in cells of XXY and XO constitution as well. Hence, if the two constricted chromosomes seen in some cells are homologous they cannot be the X chromosomes. If the constricted chromosomes are non-homologous autosomes, this represents the first suggestion of homologous human autosomes which are morphologically different.

With present-day resources, I am disinclined to number the constricted chromosomes according to size. The identification of all the chromosomes of the group 6–12 may be done almost as well or as badly by eye as by measurement, and is too arbitrary to allow any far-reaching conclusions to be drawn.

My interpretation of the findings is as follows: one of the biggest and most acrocentric chromosomes of the group 6–12 is characterised by a secondary constriction. A less obvious constriction of the same type is seen occasionally in one of the chromosomes no. 1 and in another, perhaps smaller, chromosome of group 6–12. At this stage of the work, the clearly constricted chromosome cannot be better defined, and we must remember that it may be an X chromosome. It is impossible to offer a definite explanation of its genesis, and the significance is also obscure.

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THE DENVER CLASSIFICATION AND GROUP III

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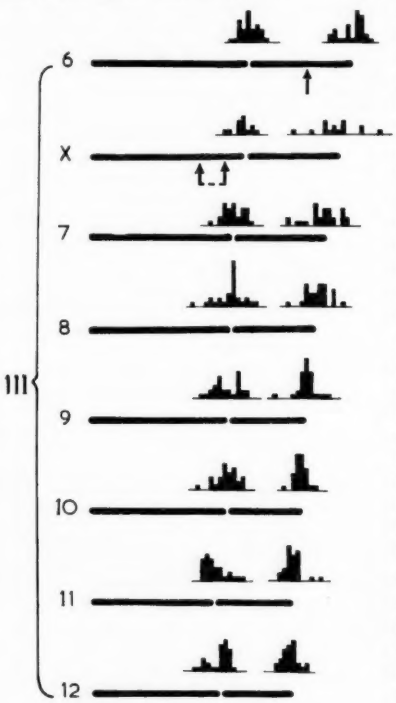
IN the Denver classification of human chromosomes (1960), group III consists of larger metacentric chromosomes with the serial numbers—6, X, 7, 8, 9, 10, 11, 12—arranged according to size.

Chromosome 6 is a definite entity, not only being distinctly larger than the others but also possessing a narrow secondary constriction or band midway in the short arm (unpublished observations by Dr. J. L. Hayward and ourselves). Levan (1959) first placed this chromosome with 4 and 5 in group II.

Chromosomes 11 and 12 are small enough to be separated from the remainder. As a rule, the pair with the shortest short arm is placed as no. 12, but whether the total length of this pair is shorter or longer than no. 11 is perhaps difficult to say.

The other chromosomes in the group—X, 7, 8, 9, 10—represent a problem due to their even sizes, although they are usually arranged in descending order. When emphasis is placed on pairing up the chromosomes, one finds in the male that the unpaired chromosome shows a greater variation in size than the others—a feature to be expected from knowledge of the sex chromosomes in animals. Thus one does not have to interpret this as due to any unreliability in pairing up homologous chromosomes, although it must weaken the validity of pairing up these chromosomes in females or subjects with supernumerary X chromosomes. But the "convention of the Barr body" helps this situation because it implies that the number of X chromosomes equals the number of Barr bodies plus one. Abnormalities



Group-III karyogram based on 28 assessments from 14 cells selected during a study involving analysis of 2000 cells from one individual. The arrows denote pale-staining gaps.

of the X chromosome may be seen from variation in size of the Barr body (this use of the Barr body is exemplified by Jacobs et al. 1960).

Among the larger chromosomes in the group there is one which shows a large pale gap in its long arm, immediately adjacent to the centromere, which is seen with difficulty in blood culture. This chromosome is usually single; but, when occasionally two are found, they are not obviously identical. There may well be a case for considering this as the X chromosome. It is not detectable in all cells, and it appears equally often in males and females; it may be the X chromosome which does not form the Barr body, hence its singleness in both sexes. The other X chromosome in the female (forming the Barr body) should be without distinction in condensation in metaphase. We are trying to obtain data on this chromosome by labelling with tritiated thymidine, which should differentiate in time between the synthesis of desoxyribose nucleic acid in heterochromatin and in euchromatin.

We have adopted the following procedure when dealing with problems concerning group III. First we arrange the chromosomes (enlarged cut-out photographs) *in pairs* according to shape, mass, and particular features; the two homologous chromosomes in a pair are placed underneath each other; and then the pairs are arranged according to *size*. In a male, one of the chromosomes will be unpaired—this we may assume is the X chromosome. When the chromosome lengths are expressed as a percentage of the total length of each row (normalised), the presumed X chromosome is not included in either total, although its percentage length is calculated from the mean of these totals. The unpaired chromosome often fits the second position in the group (between 6 and 7), although it shows more variation than the others, as one expects.

Accepting this position for the X chromosome, a normal female complement is dealt with in a similar way to the male, assuming again that the X chromosome pair will be next to no. 6 in size. Similarly, one would deal with supernumerary X chromosomes.

In cells " normalised " in this way we have noticed that chromosome 10 often has a more median centromere than 9. In triploid cells improvement in pairing of homologues may be possible, where there are obvious similarities between two of the three homologues (Penrose and Delhanty 1961). Two haploid rows will then be correctly established (i.e., no two homologues in the same row), and one is faced only with matching the third set (which is *known* to be haploid) in the correct position, having two homologues for comparison already. Polyploid cells in general show less variation between homologues than between cells, and therefore arrangement of chromosomes in the group is simplified.

In addition to these considerations, one can occasionally recognise sex chromosomes by heteropyknotic behaviour. This is most convincingly demonstrated by increased staining of the X and Y, but this feature is by no means constant and it may only occasionally decide a controversial issue.

Since the length of a chromosome must be related to its genic contents, it is improbable that two non-homologous chromosomes in the group would have exactly the same length; but, owing to the heterogeneity of the human species, many " normal " people may have different-sized chromosomes belonging to the " same " pair.

References at foot of next column

AN UNUSUALLY LONG HUMAN Y CHROMOSOME

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DURING a survey of a number of apparently normal human subjects as candidates for an experiment, one man was found to have an unusual Y chromosome:

He is an apparently normal Caucasian, aged 30, who has both male and female offspring. A peripheral blood sample was taken, and prepared by a modification of the method of Moorhead et al. (1960). Although the karyotype was otherwise unremarkable, the Y chromosome was longer than usual. This feature of the karyotype was found constantly in the hundred cells examined.

Although the usual human Y tends to vary in length (in relation to the other chromosomes), it is normally

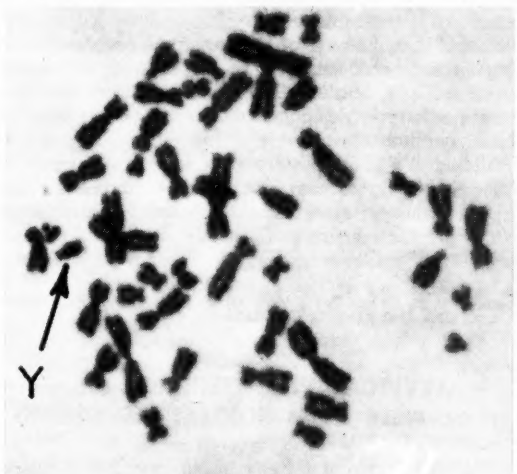

Fig. 1—Cultured leucocyte in metaphase, showing the unusually long Y chromosome.

Fig. 2—Y chromosomes compared with smallest metacentrics: *(a)* subject with long Y; and *(b)* normal subjects.

about the same length as the smallest metacentric (numbered 20, Denver Classification 1960), or very slightly longer. The subject's Y was always rather longer than the small metacentric, and, in addition, it usually appeared to be somewhat heteropyknotic. Fig. 1 shows chromosomes

* Operated by the Union Carbide Corporation for the U.S. Atomic Energy Commission.

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of a cultured peripheral leucocyte in metaphase. The Y chromosome and smallest metacentric from this subject and several others with typical Y chromosomes are compared in fig. 2. Because of the inherent variability of chromosome length between cells, it would be extremely difficult to state quantitatively how much longer the subject's Y chromosome is than the usual Y. Subjectively, the increase appears to be about 15%.

In our own observations, and those of others with whom we have discussed the matter, the length of the human Y chromosome varies not only in different cells from the same individual but also between different individuals. Probably these variations are simply a reflection of the largely heterochromatic nature of the Y chromosome. Whether the extra length in the present case is the result of extra chromatin length, in the form perhaps of a translocated fragment, cannot be decided at present. It seems unlikely, however, that there is any duplication of euchromatin in the karyotype, in view of the subject's normal phenotype. The extra length may be due either to less contraction of the normal length of chromatin or to the addition of heterochromatic length.

We feel that, because of the variations encountered in the lengths of particular chromosomes between and within normal subjects, caution should be exercised in assuming that minor karyotypic anomalies are necessarily related to clinical symptoms.

Summary

A human Y chromosome of unusual length is described. The man who possesses this chromosome has no obvious phenotypic abnormality.

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ATYPICAL PHENYLKETONURIA IN SISTERS WITH NORMAL OFFSPRING

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PHENYLKETONURIA is an inborn error of metabolism which is almost invariably associated, in the untreated, with mental deficiency. Of the reported cases, the great majority are idiots (I.Q. <20), and nearly all the rest are imbeciles (I.Q. <50); only 2% have an I.Q. greater than 60 (Knox 1960). A small number of phenylketonurics have intelligence ranging from I.Q. 75 to 120 (Coates, Norman, and Woolf 1957; Sutherland et al. 1960). These patients appear to form a special group in which some specific factor protects the central nervous system from the effects of the metabolic error.

We here describe a family in which two sisters were shown to have phenylketonuria. These two women had, between them, six children whose clinical and metabolic status has been studied.

Case-reports

Case 1.—A woman, aged 30, who had diabetes mellitus, was found to be excreting phenylpyruvic acid on a routine urine test with ferric chloride. She was at this time 16 weeks pregnant. Her diabetes was well controlled with insulin zinc suspension, and she was otherwise a healthy young housewife and mother. She had attended a grammar school and obtained the general school certificate examination with 3 credits and 2 passes. She had shown no behaviour disorder at any time, and she coped remarkably well with her large and active family. There was no history of mental or neurological disorder.

She and her children were brought to the Park Hospital for Children for investigation. Chemical examination of her blood and urine by one of us (L. I. W.) confirmed the diagnosis of phenylketonuria. Her I.Q. on the Wechsler adult intelligence scale was 102. An electroencephalogram (E.E.G.) showed no abnormality.

She was followed until 7 months after the birth of the child she was carrying, and she continued to excrete phenylpyruvic acid. A phenylalanine-tolerance test some months after the birth gave a result similar to that found in other phenylketonurics, except that the initial concentration of phenylalanine in the blood-serum, after a fast of 7 hours, was only 8·5 mg. per 100 ml. The concentration of blood-tyrosine did not rise after a loading dose of phenylalanine.

The Children

The four other children were pleasant well-behaved girls, aged 11 years 3 months, 8 years 8 months, 7 years 3 months, and 3 years 9 months. They showed no neurological abnormalities, and their E.E.G.s were within normal limits. The eldest had passed the 11-plus examination, and she was attending a grammar school; the next two attended an ordinary primary school without showing any scholastic difficulties. The youngest had an I.Q. of 101 on the Terman-Merrill scale.

The fifth child was born by cæsarean section on August 26, 1960, 21 weeks after phenylpyruvic acid was first detected in the mother's urine. The period of gestation was 37 weeks. The amniotic fluid, cord blood, and first specimen of urine passed by the infant contained phenylalanine in high concentration. The infant excreted *o*-hydroxyphenylacetic acid, in decreasing amounts for a few days, after which her urine became normal in all respects (the concentration of phenylalanine in the urine dropped to normal within 48 hours of birth). The infant appeared to be clinically normal at birth, and she continued to develop normally. Dr. Ruth Griffiths determined the baby's general intelligence quotient at the age of 3 months, and found a G.Q. of 95. An E.E.G. showed no abnormality.

The parents of the patient were unrelated. Phenylalanine-tolerance tests gave results, in both parents, similar to those seen in heterozygotes for phenylketonuria (Hsia et al. 1957). This finding tends to confirm that the patient's disorder is the expression of a pair of recessive genes. Specimens of urine from her parents and from her four sisters were examined. One sister was found to excrete considerable amounts of phenylalanine and *o*-hydroxyphenylacetic acid. This lady is reported below (case 2).

Case 2.—The patient was a married woman, aged 25, who had a history of epileptic seizures starting at the age of 9 years. The seizures were at first frequent—once or twice a week—and were grand-mal type, lasting about half an hour. They became progressively much less frequent and of shorter duration, and they finally stopped at the age of 23. Her mother thought that she had deteriorated during this period from being the brightest to the dullest member of the family. She and her son were brought to the Park Hospital for Children for investigation.

Routine tests for phenylpyruvic acid in her urine (ferric chloride, ' Phenistix ', 2:4-dinitrophenylhydrazine) were consistently negative, but it could be detected by the more sensitive technique of paper chromatography. Her blood-phenylalanine level (9·9 mg. per 100 ml. after a fast of 12 hours) was several times the normal, and her response to a phenylalanine-tolerance test was typical of a phenylketonuric, with no rise of blood-tyrosine concentration. She excreted large amounts of phenylpyruvic acid after a loading dose of phenylalanine.

The Wechsler adult intelligence scale gave an overall I.Q. of 83, with verbal scores within the normal range and non-verbal scores at a feeble-minded level. There were also qualitative indications of brain damage.

An E.E.G. recorded when fasting showed some abnormality, with rhythmic 6 c.p.s. theta activity in the resting tracing, and a few random arrythmic delta bursts on over-breathing. A second E.E.G., $1^1/_2$ hours after taking L-phenylalanine (0·1 g. per kg. body-weight), showed a very different picture. During the resting period an increase in slow activity was seen. At irregular intervals there were minor paroxysms of arrhythmic slow waves at about 3 c.p.s., some showing a near wave-and-spike pattern. During overbreathing these paroxysms increased in number and voltage. Some of the bursts were unilateral but both hemispheres were affected indifferently.

This patient's son, aged $3^1/_2$ years, appears to be developing normally. The results of a phenylalanine-tolerance test were similar to those given by heterozygotes for phenylketonuria (Hsia et al. 1957).

Discussion

The success of a diet low in phenylalanine in preventing mental deterioration, and, in some cases, in reversing E.E.G. changes in those afflicted seems to confirm the intoxication theory of phenylketonuria. Most mentally normal phenylketonurics have a concentration of phenylalanine in the blood, or of phenylpyruvic acid in the urine, which is lower than is usually found in phenylketonuria although far higher than in the normal subject (Sutherland et al. 1960). Both the affected women reported here had a relatively low concentration of phenylalanine in the blood; but this was not necessarily constant throughout their lives.

The clinical and biochemical findings in case 2 would fit the following hypothetical sequence of events: a relatively low concentration of phenylalanine up to the age of 9 years, then a rise leading to brain damage, epilepsy, and mental deterioration, which was followed, at some time between the ages of 9 and 25 years, by a fall in phenylalanine level. A loading dose of phenylalanine altered the E.E.G. pattern strikingly, suggesting that although the patient is no longer deteriorating and her epilepsy is in remission, yet her cerebral function is still liable to be impaired by the metabolic error; for a normal subject showed no change in the E.E.G. after a similar dose of phenylalanine.

Case 2 raises an important problem in the diagnosis of phenylketonuria; by the simple tests usually applied the patient did not appear to be a phenylketonuric, though more elaborate investigations left no room for doubt. This condition, which may be termed " occult phenylketonuria ", has only once before been reported (Herbordt-Günnsel 1954). Its frequency is unknown and would not be easy to determine.

The six children of these two sisters were presumably exposed, in utero, to abnormal concentrations of the substances circulating in their mothers' blood. In case 1 the last-born daughter was certainly exposed, for the last 21 weeks of the pregnancy, to levels of phenylalanine, &c., much higher than normal. One might expect the brain of a fœtus developing in a phenylketonuric milieu to be damaged, resulting in a non-phenylketonuric mental defective. Although the women reported here were atypical phenylketonurics, the fœtuses were exposed to high concentrations of the same chemical substances as in lower-grade phenylketonuric mothers. This suggests that there is no biochemical reason why any phenylketonuric woman should not have normal children.

Without doubt genetic factors are operating to render the phenylketonuria atypical in these two sisters, particularly as there are no low-grade phenylketonurics in their sibship. The existence of a third allele, in addition to the normal gene and the gene for phenylketonuria, has been suggested (Coates, Norman, and Woolf 1957); this third type of gene would synthesise a protein with weak enzymic properties–i.e., it would convert phenylalanine to tyrosine much more slowly than the enzyme synthesised by the normal gene, but much faster than the inactive protein synthesised by the gene for phenylketonuria—thus producing a " partial metabolic block ". Against this theory is the failure of the blood-tyrosine concentration to rise after feeding phenylalanine to the patients reported here; a similar finding has been made in two other unrelated high-grade phenylketonurics of I.Q. 109 and 97 respectively (L. I. Woolf, to be published). The results of phenylalanine-tolerance tests in the parents of the patient we describe also suggest that only two alleles are involved. An alternative theory is the inheritance of a " modifier " gene which, acting in some unknown way, reduces the blood phenylalanine concentration and so reduces, or completely prevents, damage to the brain. Further work on this and other aspects is continuing, and full details will be published shortly.

Summary

Two phenylketonuric sisters appeared to have an unusual variant of the disease, with minimal damage to the central nervous system.

Phenylpyruvic acid in the urine of one of them could be detected only by means of paper chromatography. No phenylalanine hydroxylase activity could be detected in either sister.

None of their six children is mentally defective despite exposure to a phenylketonuric environment while in utero.

We wish to thank Dr. A. B. Stratton for permitting us to study his patients and for the very active part he played in the investigations. Dr. Victoria Smallpeice, Mr. K. Renton, and Mr. P. Lockwood first found phenylpyruvic acid in the urine. Mr. M. G. Day, Mrs. A. Lorenzen, Mrs. V. Tymms, and Mr. B. Goodwin gave expert assistance in the laboratory. The nurses of Park Hospital for Children, the Churchill Hospital, and the South Devon and East Cornwall Hospital were most patient and helpful during the investigations.

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". . . The advancement of learning depends on the deliberate cultivation of the imaginative activity of the mind. There is no substitute for it. There is no rigorous and foolproof device by which one can arrive at, and prove, general truths. Scientists are not cold and calculating men whose business it is to crank the machine of discovery which will give them the right answers. Research is a most passionate enterprise . . ."—Prof. P. B. MEDAWAR, at a degree congregation in the University of Birmingham. *Birmingham Post*, July 15, 1961.

Preliminary Communication

RESPIRATORY SYNCYTIAL VIRUS IN BRITAIN

IN 1956, a virus indistinguishable from chimpanzee coryza agent was isolated from human patients with bronchopneumonia and croup.[1] Chanock and Finberg suggested that this group be renamed respiratory syncytial (RS) virus.[2]

The ætiological role of RS virus in lower-respiratory infections in infants and young children, and upper-respiratory infections in older children and adults, has been further elucidated by Chanock and his colleagues,[3–6] and by McClelland and her colleagues.[7 8] The subject has recently been reviewed elsewhere.[9]

In the winter of 1961, an outbreak of bronchiolitis in infants occurred in Bristol, and we received throat swabs from several of the cases admitted to hospital. From two patients, Gwilliam aged 7 months and Nutt aged 6 months, viruses were isolated which were indistinguishable from RS virus.

VIRUS ISOLATION

Throat swabs were taken into 50% milk-saline, and primary isolation was effected in HeLa cells. In one case the specimen was frozen before being inoculated. The cytopathic picture consisted of large round cells and of syncytia, sometimes very large and striking. Numbers of small, round, refractile cells were also always present. The entire cell sheet was affected 4 or 5 days after the cytopathic effect first appeared.

Examination of stained preparations showed large numbers of eosinophilic cytoplasmic inclusions in affected cells (see figure). Intranuclear inclusions were originally described with RS virus [1] but Chanock has since observed cytoplasmic inclusions.[10]

OTHER PROPERTIES

Neither isolate produced hæmadsorption or hæmagglutination with human, guineapig, or chicken erythrocytes at 4°C, room temperature, or 37°C.

The Gwilliam virus was intermediate in its sensitivity to ether. 20% ether for 20 hours at 4°C resulted in a 100-fold loss of infectivity compared with the control.

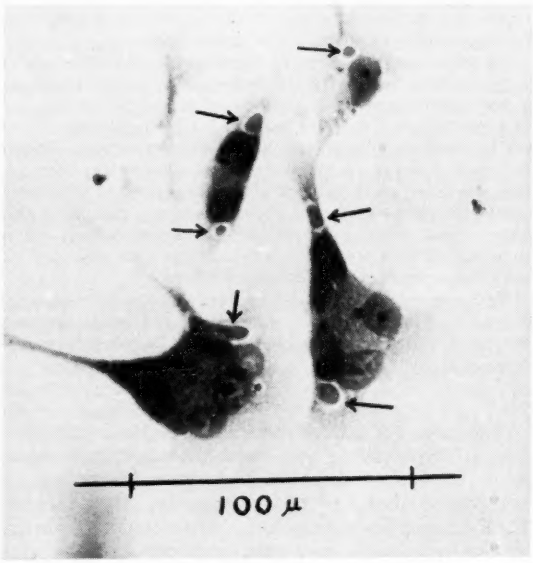
SEROLOGICAL STUDIES

17 out of 20 sera, submitted to this laboratory for Wassermann reaction, fixed complement in the presence of tissue-culture fluid infected with Gwilliam virus. 10 of these sera were also tested against Nutt and against a strain of RS virus (Randall) isolated in Chicago by Beem et al.[11] The three viruses showed an identical pattern of antibody titres.

A paired serum from an American patient of Dr. Hamre's with an RS virus infection showed a rise in neutralising antibody titre to Gwilliam and Randall. Further, Gwilliam was neutralised to the same titre as Randall by a guineapig antiserum, prepared by Dekking against a virus (Boshardt) isolated by him in Holland in 1958.[12] This virus was known to give rise to syncytia in tissue culture, to form cytoplasmic inclusions, and to be intermediate in its sensitivity to ether.[13]

DISCUSSION

A virus indistinguishable from the RS virus of Chanock has been isolated from two cases of bronchiolitis in infants. The American strain of RS virus was not received



HeLa-cell tissue culture infected with Gwilliam virus showing intracytoplasmic inclusions. (Hæmatoxylin and eosin.)

in this laboratory until after most of the work reported in this paper was finished. The cytopathic effect in HeLa tissue cultures is quite striking. It is therefore not easy to understand why the virus has not previously been isolated in this country. In part, the explanation is that the virus is highly susceptible to freezing and thawing.[11] Thus Chanock et al.[3] point out that from October, 1959, to February, 1960, they isolated only 4 strains. After adopting the method of inoculating tissue cultures without first freezing specimens, they isolated 60 strains in the 5 months, March to July, 1960. The medium into which the throat swab is taken also seems to play a part.[14] It may also be that strains of any particular cell line vary in their susceptibility to this virus. The finding that a high proportion of adult sera contain antibodies to RS virus suggests that infection with this virus may be as widespread in this country as it is in North America.

We are grateful to Dr. D. A. J. Tyrrell for helpful suggestions and supplies of Boshardt antiserum, and to Dr. D. Taylor-Robinson for the Randall strain of RS virus and the paired sera from the case of RS infection.

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Reviews of Books

System of Ophthalmology

Vol. II. *The Anatomy of the Visual System.* Sir STEWART DUKE-ELDER, G.C.V.O., F.R.S., KENNETH C. WYBAR, B.SC., M.D., CH.M., F.R.C.S., lecturer in ophthalmology, University of London, ophthalmic surgeon, Moorfields Eye Hospital and the Royal Marsden Hospital. London: Henry Kimpton. 1961. Pp. 901. 130*s.*

THE eye is unique in that, while postmortem changes and the need for magnifying techniques make its anatomy hard to demonstrate in the dissecting-room, much of its more important anatomical details can be inspected in vivo under a useful degree of magnification. It is not surprising, therefore, that knowledge of the anatomy of the eye should have lagged behind that of the rest of the body and that optical methods of examination (chiefly the slit-lamp microscope and the gonioscope) should have played so large a part in the expansion of knowledge in the past fifty years. It is understandable, too, that, while professional anatomists have laid the foundations of this knowledge, its final presentation often rests with the ophthalmic surgeon.

This survey forms the second volume of the projected *System of Ophthalmology* and includes, as well as the eye, its adnexa, and the orbit, an extensive section dealing with the motor, sensory, and autonomic systems associated with vision. Its first section, on the historical development of the anatomy of the eye and of the central visual system, is an illuminating introduction to the remaining three sections dealing with the anatomy proper.

In general, the classical presentation of regional anatomy is used, with illustrations from standard anatomy textbooks; but these are amplified, in many chapters, by extensive reference to recent work from a wide variety of sources, many of them ophthalmological. When dealing with the ocular blood-vessels, this is especially valuable, and this section includes excellent illustrations of the vascular system displayed by the neoprene injection technique. The chapter devoted to the anterior chamber is particularly welcome, because it sets out the great amount of new detail from recent work on the canal of Schlemm and its communicating channels, by observation of the aqueous veins and by gonioscopy. The chapter on the retina, written in conjunction with Dr. Katharine Tansley, and integrating with classical work on the subject (her own and that of Polyak), is outstanding and gives a comprehensive appraisal of present knowledge.

A copy of this work will be found essential for the library of every ophthalmological centre.

Angiography

Editor: HERBERT L. ABRAMS, associate professor of radiology; director, division of diagnostic radiology, Stanford University School of Medicine, Stanford, California. London: J. & A. Churchill. 1961. 2 vols. Pp. 807. 340*s.*

CONTRAST angiography now has an accepted place in the investigation of disease of the aorta and peripheral vessels; and improved techniques and contrast media, as well as increased understanding of the risks, have reduced the hazard of this procedure. By giving in one book an up-to-date account of the practice of angiography Dr. Abrams and his international team have made a most useful contribution. They have covered the subject in a thorough and practical way, neglecting little of importance. The style is discussive rather than dogmatic. The value of each investigation is assessed against the known risks, and other methods of investigation are reviewed. Each writer gives a clear exposition of his topic, and the illustrations are mostly good.

This book will be highly prized, for nowhere else can a comprehensive account of this subject be found under a single cover. It will be doubly prized because each section is complete in itself and can be read without reference to the book as a whole.

Injuries and Infections of the Hand

ROBERT H. C. ROBINS, M.A., M.B., F.R.C.S., consultant orthopædic surgeon, Royal Cornwall Infirmary, Truro. London: Edward Arnold. 1961. Pp. 220. 63*s.*

JUST as orthopædic surgery was once almost synonymous with the surgery of tuberculous joints, so hand surgery was until recently concerned mainly with the treatment of infected fingers. It is still not known why the swollen suppurating hands, to be seen in such large numbers in any casualty department twenty years ago, have almost disappeared: certainly the introduction of antibiotics is not the whole explanation More than half of Iselin's book on *Surgery of the Hand*, published in 1940, was devoted to acute infections. In the present volume this topic is dismissed in 23 pages. Iselin, describing a series of periungual whitlows, was proud to report that amputation of part of the finger had been necessary in less than 12% of his cases. In the pages on infection which Mr. Robins has written the word amputation is not to be found.

This work, though it contains several introductory chapters on anatomy and the general principles of treatment, deals very largely with major hand injuries and with reparative procedures outside the field of the casualty officer or the occasional hand surgeon. The text, and the many illustrations, are so lucid that no student or doctor will find them at all difficult to follow. But it is the surgeon who already has basic experience in orthopædic and plastic techniques who will appreciate this book most.

The Chemical Basis of Clinical Psychiatry

A. HOFFER, M.D., psychiatric research division, department of public health, University Hospital, Saskatoon, Saskatchewan; HUMPHREY OSMOND, M.R.C.S., D.P.M., department of public health, psychiatric research division, Saskatchewan Hospital, Weyburn, Saskatchewan. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 277. 68*s.*

THE authors of this book have long been pioneers of a chemical theory of schizophrenia, and they offer the most clear, comprehensive, and scholarly account of the subject that has yet appeared. Especially interesting is the attempt to link their own rather tenuous theories of adrenaline derivatives with the taraxen theory of schizophrenia. Though they claim to review anxiety, depression, schizophrenia, and the model psychoses, the subject is by no means fully described—for example, Gjessing's observations are omitted, as are the electrolyte changes associated with depression and E.C.T. And the reader should beware of partisan and selective passages. Not all the criticisms of the main theory have been fully discussed (for example, that of Feldstein [1]); and, of course, in this rapidly growing subject a great deal of new material has appeared even since 1960. But as a source of important, stimulating, and, above all, logical ideas the work is compulsory reading for those concerned with the origins of these disorders.

Essentials of Human Embryology

FRANK D. ALLAN, M.S., PH.D., associate professor of anatomy, George Washington University School of Medicine, Washington, D.C. New York and London: Oxford University Press. 1960. Pp. 225. 40*s.*

THIS book, dedicated to "belabored students and their time-pressed instructors", makes no pretence at being more than a synopsis of the subject and has the virtue of leaving the reader in no doubt about the need for further reading elsewhere. The text is in outline form and is liberally supported by line drawings. The trouble is that the educative value of embryology is lost unless the wherefores and whys of the subject are explained, unless adult morphology is made to make sense, and unless the relevance of embryology to clinical medicine is made clear.

Fig. 7a is misleading in that it shows the implanting blastocyst as floating in a cavity in the endometrium; and some of the figures showing the development of the external genitalia are inaccurate. The author's method of relating the time of

1. Feldstein, A. *Amer. J. Psychiat.* 1959, **116**, 454.

ovulation to the previous menstrual period is not the one generally accepted. A long list is given of methods used to demonstrate the time of ovulation in a woman, but no reason is given for wanting to know the time of ovulation. The descriptions of the development of the vagina and of the urethra are considerably out of date. The relationships of the arteries and veins in the head and neck are not explained. There is no mention of gastrulation, nor is there a clear exposition of how the corresponding processes in man are responsible for laying down the embryonic axis and how these developmental processes are related to the causation of Siamese twinning. The text does not refer to sex chromatin or to chromosome counts in relation to sexual and other abnormalities of development. Maternal age is not included as a factor in the causation of congenital malformations, and rubella is mentioned only in connection with eye deformities.

Despite these shortcomings, the book will undoubtedly be welcomed by the student whose sole aim is to work up the subject for examinations, and it may help him to grasp certain aspects of embryology.

Handicapped Children

JOHN D. KERSHAW, M.D., B.S., M.R.C.S., D.P.H., medical officer of health, Colchester. London: William Heinemann. 1961. Pp. 228. 21*s*.

THIS book appears to be the result of many years of thought and study. The first seven chapters discuss general topics such as the parent's and public's attitudes to the handicapped child, education, employment and recreation, and the principles of assessment. The following ten chapters deal with particular handicaps such as blindness or deafness. (Two rather important handicaps—spina bifida and speech defects—are omitted.) Each chapter on a physical handicap is divided into sections under the headings of causation, clinical picture, diagnosis and assessment, treatment and management, education, and future prospect. Generally the text on all these aspects is full. Inevitably the clinical details are short, and sometimes they may mislead. Pædiatricians would question some statements such as "most children have 'convulsions' of some sort in the first two years of life"; "the worst way to make assessments [in cerebral palsy] is by applying intelligence tests in a clinic"; and "mentally handicapped children will be more disturbed by the fit of an epileptic schoolfellow than the mentally normal children". This volume will be a source of information and opinion to a variety of workers with handicapped children, including school medical officers, pædiatricians, teachers in special schools, and youth employment officers. Members of interested voluntary societies would benefit by reading here an overall account of each handicap, and of all the problems that are likely to arise.

Blood and other Body-Fluids

Analysis and compilation. Compiled by PHILIP L. ALTMAN. Editor: DOROTHY S. DITTMER. Washington, D.C.: Federation of American Societies for Experimental Biology. 1961. Pp. 540. $10.

THIS is a unique compilation of quantitative information about every aspect of blood and body-fluids. It includes a revision of the handbook on Standard Values in Blood published in 1952. For ease of reference the book is divided into 25 sections. The first 12 are concerned with blood, the other 13 with body-fluids including sections on nerve electrolytes and water content, fluids during pregnancy, and fluids of ear and eye. The data have been obtained from the published work, checked by personal communication, of workers all over the world, and references are given throughout. Data are given not only for man but also for domestic and laboratory animals and some birds and reptiles. Information about the hæmolymph of insects, crustaceans, and molluscs is included. The section about the water excretion of aquatic amphibians and fishes is fascinating. (How does one catheterise the Dolphin [*Tursiops truncatus*] or the fasting carp [*Cyprinus carpro*]?) There is a colour plate of the normal blood and marrow cells in man, and a valiant effort is made to explain current ideas on blood coagulation by means of diagrams.

Every biological worker, including all doctors who work in routine or research laboratories, is indebted to the Committee on Biological Handbooks and its staff for producing so comprehensive a volume.

The Older Patient

Editor: WINGATE M. JOHNSON, M.D., chief of staff, private diagnostic clinic, and professor of clinical medicine, Bowman Gray School of Medicine of Wake Forest College. New York: Paul B. Hoeber. 1960. Pp. 589. $14·50.

THIS book represents a praiseworthy attempt to provide for the general practitioner a guide to the practice of medicine among elderly patients. It contains 26 articles by 21 authors covering the general aspects of ageing, retirement, and adjustment to advancing years, as well as reviews of the disorders of each system as they affect the elderly. The relief of pain by analgesics and by local methods of nerve-block is reviewed, and surgery in the elderly is not overlooked. Some of the best chapters are the more general ones by Dr. Johnson, and the account of the mental disorders of the ageing is especially good. On the whole, however, the quality is uneven; and at least for British readers a really good book on this important subject has still to be written.

Your Heart

A Handbook for Laymen. H. M. MARVIN, M.D., associate clinical professor of medicine, Yale University School of Medicine. London: Hodder & Stoughton. Pp. 303. 21*s*.

Dr. Marvin has written to instruct the non-medical reader, but his book is full of interest for many doctors. It is in the tradition of the best modern popular scientific book—remarkably full in its treatment, well written, in an attractive personal way, without a lot of pretentious technicalities, and intelligibly presented. The main facts of the structure and function of the cardiovascular system are described, and on this foundation is built an admirable systematic account of the disorders of the system. Some may wonder whether the layman need be informed quite so fully: for example, is there cause to mention the Wolff-Parkinson-White syndrome? Yet the syndrome is used as an aid in describing the mechanisms underlying paroxysmal tachycardia; and this gives a clue to the style of the whole book. Each chapter deals with the common manifestations of heart-disease, emphasising the practical points which arise in management; where relevant the epidemiology, ætiological factors, and other matters of general interest are reviewed. Such discussions can be informative and helpful to doctors. The discussion on the rationale of the usual methods of treatment includes valuable commentaries on such matters as diet in coronary atherosclerosis.

Textbook of Medical Treatment (8th ed. Edinburgh: E. & S. Livingstone. 1961. Pp. 983. 60*s*.).—This book, edited by Sir Derrick Dunlop, Sir Stanley Davidson, and Prof. Stanley Alstead, has enjoyed an enviable reputation for over twenty years; for it embodies all that is best in the Scottish tradition of medicine and therapeutics. The new edition is full of vigour. Much has been rewritten by younger hands, and there are new sections on diseases of the eye and on the relief of pain. The latter is, however, a little disappointing in that it says nothing about the possibilities of surgery, of intrathecal treatment, or of the latest morphine substitutes—a subject on which authoritative guidance would be welcomed by many. A particularly happy feature is the excellent chapter on the care of old people, which includes a list of the equipment required for a geriatric unit and the names of the firms who supply this. A merit of this book has always been that it is no mere guide to applied pharmacology but emphasises management and treatment of the patient as a whole—a feature that is well maintained in the present edition. It will be equally valuable to those practising in general practice and in hospital.

THE LANCET

LONDON 26 AUGUST 1961

What Price Safety?

IF danger is sweet, as HORACE professed, life on the roads is becoming sweeter every day. In terms of physical energy a family saloon travelling at fifty miles an hour corresponds to 100 Service rifles, and our modern highways are the equivalents of Napoleonic battlefields. "It is unique in civilian life for so many individuals (of varying temperaments, aspirations, and competence) to have independent control of so much energy", Dr. J. P. BULL said in a recent broadcast talk, "and it is not surprising that this energy sometimes gets out of hand". It is true, of course, that, when the number of casualties is calculated as a proportion of those exposed to risk, road-traffic emerges as a very gentlemanly battle (or as an exceedingly mild epidemic); but in absolute numbers it has grown into one of the great public-health problems of the age. At the core of this problem lies a seemingly simple question, which in turn raises two further questions: Are safe drivers born or made? In so far as they are born, how can they be selected? In so far as they are made, how can one make them? All three questions are, in fact, extremely difficult to answer; but at least we can now draw on carefully compiled statistical data and dispose of a good deal of fanciful speculation.

It has been recognised for many years that some drivers have more mishaps on the road than could be accounted for by chance alone; and up-to-date insurance records suggest that less than 20% of certain groups of drivers report over half the accidents. Unfortunately, growing interest in this odd distribution of road accidents has coincided with intensive study of accident proneness in industry; and some observers have jumped to the conclusion that these two entities must be closely related. That true accident proneness exists in industry is no longer in doubt. It can be demonstrated when groups of men, working in a factory under more or less identical conditions, perform a simple repetitive operation over long periods; and it correlates fairly well with certain measurable psychological traits. But car-driving is a far more complex undertaking than any of these simple tasks. To investigate accident proneness in the "driver's" sense one must study people who not only are comparable as regards age, experience, physical characteristics, and other personal details but also are exposed to roughly the same risks.

One of the first and perhaps still one of the closest approximations to a statistically ideal survey was reported from Finland, where accidents of Helsinki public-transport drivers were subjected to detailed scrutiny.[1] The results showed no correlation between the number of accidents and minor physical variables, and they gave little (if any) support to those who for many years had been trying to interpret driving ability in terms of well-defined psychological characteristics. What did emerge from the inquiry even more clearly than might have been expected was the close correlation between "accident proneness" and lack of driving experience. Drivers aged 30 had twice as many accidents as drivers aged 50; and those who had driven for less than three years had a three times higher accident-rate than those with three or more years' experience. The records of London Transport and recent studies of motor-cycle accidents show a similar trend. London Transport drivers under 30 are involved in twice as many accidents as drivers of 60; and, even within the same age-group, drivers with fourteen years' standing have half the number of accidents of those with less than four years' experience.[2] Among motor-cyclists accidents are twice as common in the first six months on the road as in any subsequent half-yearly period.[3] Compared with length of experience, even such seemingly important factors as reaction-time become insignificant: broadly speaking, the middle-aged or elderly driver is safer on the road than the young man at the height of his physical powers.[4] The main reason for this is probably that accidents are not enacted as single episodes. Getting involved in an "accident situation" and coping with the secondary effects of the initial impact are probably as important as the driver's immediate reactions; and, while young men may excel in the central act, experience will score both in avoiding and in coping with a catastrophe.

Though much of this evidence is negative, practical lessons can be learnt from it. Doctors may not need much persuasion to accept one conclusion: that driving tests are not the answer to the pedestrian's prayers. In medicine (and the parallel is not unreasonably far-fetched) we have seen a gradual shift of emphasis from rigid control of qualifying examinations to closer supervision of pre-examination training; and we might do worse than to adopt a similar approach to safe driving. Training may not be a substitute for practice, but it can provide a groundwork for its acquisition; and, at the very least, it might short-circuit the costly experience of the first few months. For training to be effective, we need to know what special skills are necessary under modern traffic conditions and how they should be taught. Much careful study is now devoted to answering the first of these two questions. Painstaking analyses of the causes of individual accidents [5] and psychometric assessment of such essential qualities as vigilance, anticipation, and judgment [6] may at first seem far removed from the hurly-burly of rush-hour traffic; but they have already yielded valuable information on such practical points as optimal speeds, braking distances, and the safety requirements of overtaking. What *does* make these data somewhat academic is not their inherent remoteness but our inability or unwillingness to make use of them. The law

1. Hakkinen, S. *Int. Congr. Occup. Hlth*, 1957.
2. Norman, L. G. *Lancet*, 1960, i, 989, 1039.
3. Scott, C., Jackson, S. Central Office of Information, SS, 277B. London, 1960.
4. Road Accidents. H.M. Stationery Office, 1958.
5. Davis, R. D. *Ergonomics*, 1959, **2**, 25.
6. Mackworth, N. H. *Spec. Rep. Ser. med. Res. Coun., Lord.* 1950, no. 268.

requires that drivers should be tested; it does not require that they should be taught. There is good evidence that expert training (such as is provided by some police driving-schools) considerably and permanently reduces the accident-rate of prospective drivers: by contrast, there is very little to suggest that driving tests are more than a marginal safeguard.

However well trained, a driver is no safer than the car which he drives; and unfortunately car designs are still firmly rooted—functionally as well as æsthetically—in the styles of the horse-drawn carriage. What was adequate visibility at a smart trot of 10 miles an hour is dangerously inadequate in a car travelling even at a modest speed; and what was a convenient "overhang" in carts drawn by two horses has become a murderous weapon in lorries driven by the equivalent of twenty. How far it is possible or indeed advisable to lay down standards of safe design is not easily decided. In the United States a recent Bill was rejected by the Senate, after having been passed by the House of Representatives. It had been firmly opposed by the Automanufacturers' Association mainly on the grounds that "to make design mandatory will restrict development rather than promote it; it will make the engineer's goal one of designing to conform to inflexible, sometimes outdated, codes . . . and it will discourage rather than stimulate research and development in automotive industry".[7] While accepting the force of this argument, we agree with the more cautious view expressed by GISSANE and BULL [8] that "it would be unrealistic to [rely on] self-regulation in the highly competitive field of selling motor vehicles". That some form of control is probably needed is suggested by their survey of Birmingham road deaths. The findings showed not only that there is room for expensive improvements in general design but also that several minor features and accessories could and should be changed at practically no cost. The needlessly narrow edge and pointed centre of cowlings of front headlamps had caused 6 fatal thoraco-abdominal injuries out of a total 149 deaths; and 2 fatal penetrating brain injuries could be attributed to the rigid pillar of the near-side front mudguard mirror (after the mirror had been knocked off). On the credit side we can confidently expect a significant reduction in both number and severity of drivers' injuries now that safety belts and harnesses not only have caught the public fancy but have also been included in the standard equipment of certain makes of cars.[9–12]

Road building is even more stringently governed by economic considerations than car design, but at least we should resist gratuitous insults to common sense. Since judgment, vigilance, and anticipation ultimately depend on the driver's ability to concentrate (as is underlined by the disproportionately high number of accidents in which cars carrying passengers, especially children, are involved), as little as possible should be allowed to distract attention. While standard international road-signs have been designed largely with this object in view, a rash of lengthy and unnecessary notices are beginning to disfigure some of our best roads. At 30 or 40 miles an hour even eloquent pleas for caution which take more than fractions of a second to read are more likely to cause than to prevent an accident.

When all has been said in favour of safe driving—and many books have been written on the subject—much truth remains in HORACE's dictum. Danger is sweet indeed; and if at times the spirit of Athos, Porthos, and Aramis seems to grip every driver, who would deny those swashbuckling fellows their spot of fun? Unfortunately only the spirit, not the circumstances, are similar. Unlike DUMAS' amiable guardsmen who (for reasons which are now, admittedly, somewhat obscure) confined themselves to murdering each other in friendly combat, their successors on the roads are not the only victims of their own high spirits. Of the 149 Birmingham road deaths reviewed by GISSANE and BULL 87 were pedestrians; and, if the series conforms with experience in the country as a whole, many of the remaining 62 were passengers. Dangerous driving is a sport which we must deny ourselves and others.

Drug-induced Gastrointestinal Bleeding

THE hazard of gastrointestinal hæmorrhage due to ingestion of drugs has received increasing attention since the observations of DOUTHWAITE and LINTOTT.[1] These workers examined 16 patients by gastroscopy after introducing aspirin into the stomach, and in 13 they noted localised hyperæmia and erosions developing around individual particles of the drug on the lesser curve. HURST [2] believed that aspirin was the principal cause of bleeding in at least half the patients with upper-gastrointestinal hæmorrhage in whom other obvious causes had been eliminated. MUIR and COSSAR [3] administered aspirin shortly before partial gastrectomy and studied the mucosal reaction in the resected stomach. They found severe changes, ranging from hyperæmia to acute ulceration, in half of 40 patients given insoluble aspirin; no reaction occurred when the residual particles of the drug had become thickly coated with mucus. MUIR and COSSAR [4] also showed that about half of a series of patients admitted to hospital with gastroduodenal bleeding had taken aspirin within forty-eight hours before their first hæmorrhage, compared with 15% of a control series. Likewise, ALVAREZ and SUMMERSKILL [5] found that, of 103 patients admitted with hæmatemesis and melæna to the Central Middlesex Hospital, 49 had taken a salicylate preparation in the previous twenty-four hours, compared with only 7 of a matched control group. They found—as did LANGE [6] and STUBBÉ [7]—a high rate of fæcal occult bleeding in relation to administration of aspirin both in patients with peptic ulceration and in controls.

Careful studies of occult blood-loss have suggested

7. Richards, K. M. *Product. Engng Bull.* 1961, **32**, 21.
8. Gissane, W., Bull, J. *Brit. med. J.* 1961, i, 1716.
9. Birrell, J. H. W. *Med. J. Aust.* 1961, i, 505.
10. Frazier, R. C. *New Engl. J. Med.* 1961, **264**, 1254.
11. Parliamentary Reports (Hansard), April 27, 1961, col. 60.
12. *Guardian*, May 30, 1961.

1. Douthwaite, A. H., Lintott, G. A. M. *Lancet*, 1938, ii, 1222.
2. Hurst, A. F. *Brit. med. J.* 1943, i, 768.
3. Muir, A., Cossar, I. A. *ibid.* 1955, ii, 7.
4. Muir, A., Cossar, I. A. *Lancet*, 1959, i. 539.
5. Alvarez, A. S., Summerskill, W. H. J. *Lancet*, 1958, ii, 920.
6. Lange, H. F. *Gastroenterology*, 1957, **33**, 770.
7. Stubbé, L. Th. F. L. *Brit. med. J.* 1958, ii, 1062.

that administration of aspirin may contribute significantly to the anæmia of rheumatoid arthritis. SCOTT et al.[8] at Hammersmith labelled patients' erythrocytes with ^{51}Cr in order to detect and measure fæcal loss of blood associated with oral administration of salicylates, corticosteroids, and other analgesics. 96 subjects were studied, including 61 with rheumatoid arthritis and 13 healthy volunteers. Aspirin caused bleeding (defined as an average daily blood-loss of more than 2 ml.) in 70% of cases, and the average daily loss in those who bled was nearly 5 ml. Similar bleeding was revealed in patients taking soluble and effervescent preparations of aspirin; nor did administration after meals diminish this tendency. On the other hand the Hammersmith workers found a much lower rate of bleeding with enteric-coated tablets of aspirin (32%); and of all salicylate preparations tested enteric-coated tablets of sodium salicylate (12%) were the least likely to cause hæmorrhage—and this without loss of therapeutic effect. Surprisingly perhaps, in view of earlier findings, oral corticosteroids were not associated with gastrointestinal bleeding, and the rate and amount of blood-loss when corticosteroids and aspirin were given together were no greater than with aspirin alone. Phenylbutazone also emerged favourably from this study, with only 1 unequivocal example of bleeding in 22 cases. Earlier, SUMMERSKILL and ALVAREZ [9] described 2 cases, both in habitual and heavy consumers of aspirin, of severe iron-deficiency anæmia of uncertain origin which responded splendidly to reduced intake of aspirin without iron medication. Further evidence of an association between ingestion of aspirin and anæmia was obtained in the Hammersmith study: in 6 cases (including 4 of rheumatoid arthritis) an iron-deficiency anæmia was thought to have been the result of long-continued aspirin consumption. Each of these 6 patients was shown to lose blood from the alimentary tract while receiving aspirin, and in each the anæmia responded to withdrawal of salicylates and oral or parenteral administration of iron.

SAVAGE [10] reviewed 910 cases of rheumatoid arthritis, collected from various centres, in which long-term steroid therapy had been given. Dyspeptic symptoms were recorded in 32%, and 12% had peptic ulceration—rates of an order not found in the steroid treatment of non-rheumatoid conditions. WEST [11] suggested that oral corticosteroids have a local action on the gastric mucosa, such as salicylates have been assumed to have. GRAY et al.[12] believed that the adrenal steroid hormones caused a sharp increase in the secretion of free hydrochloric acid and pepsin; and this view is supported by experimental work in Belfast, where CLARKE et al.[13] have shown that in dogs pharmacological doses of cortisone increase by about 50% the maximal acid secretory response to histamine of denervated gastric pouches. REID et al.[14] have found that in dogs cortisone and methylprednisolone increase the number of parietal cells in gastric mucosa also by about 50%, and they therefore feel that a cause-and-effect relation can reasonably be assumed. Nevertheless there are grounds for not accepting this view unreservedly. KAMMERER et al.[15] studied 117 patients with rheumatoid arthritis who had received oral corticosteroids. In 36 a peptic ulcer developed; in 31 the ulcers were gastric, and the majority were on the greater curve. This predominantly gastric localisation suggests that factors other than those commonly thought to lead to peptic ulceration are involved. Moreover, in 14 healthy volunteers corticosteroid administration caused no significant change in the secretion of acid and pepsin. The fact that impaired mucosal resistance has so far defied quantification has probably deterred investigators; but, in the formation of ulcers related to administration of corticosteroids, changes in the properties or rate of production of gastric mucus may play as important a part as the levels of pepsin or free hydrochloric acid.

Some practical lessons can be drawn from all these observations. Consumption of aspirin is an important cause of gastroduodenal bleeding and makes an appreciable contribution to the number of hospital admissions on account of hæmatemesis and melæna. Patients with peptic ulcers should be counselled against taking aspirin for the relief of incidental discomforts; and, where aspirin must be taken, this should be in enteric-coated tablets. Whatever the primary disorder, where long-term administration of aspirin is undertaken, this should be accompanied by periodic hæmoglobin estimations and, where necessary, by iron supplements; and tests for occult blood may help to distinguish patients who bleed severely when aspirin is taken and for whom the enteric-coated preparations may be safer. As regards corticosteroids, the mechanism by which these induce alimentary lesions is still undecided; but, despite the negative findings in the Hammersmith trial, the gastric mucosa of patients with rheumatoid arthritis seems to be especially vulnerable to this group of drugs; and accordingly so long as these drugs are administered close watch should be kept for melæna or other indication of a gastric lesion.

Work for Prisoners

ONE thing on which penologists are likely to agree is that prison rehabilitation requires realistic, intensive, and constructive work. The Home Office—which has certainly not disputed this view for many years—has strengthened it by issuing the first report of its Advisory Council on the Employment of Prisoners.[16] In its first year the Council has concentrated on what should be done inside prisons, pointing first to the obvious difficulties posed by gross overcrowding, old inadequate premises, shortage of prison officers, and high labour turnover, which limit some local prisons to a working week of only sixteen hours. The Council says sensibly that every person (including every prisoner) should make the best contribution he can to the community,

8. Scott, J. T., Porter, I. H., Lewis, S. M., Dixon, A. St. J. *Quart. J. Med.* 1961, **30**, 167.
9. Summerskill, W. H. J., Alvarez, A. S. *Lancet*, 1958, ii, 925.
10. Savage, O. *ibid.* 1959, ii, 785.
11. West, H. F. *Brit. med. J.* 1959, ii, 680.
12. Gray, S. J., Benson, J. A., Jr., Spiro, H. M., Reifenstein, R. W. *Gastroenterology*, 1951, **19**, 658.
13. Clarke, S. D., Neill, D. W., Welbourn, R. B. *Gut*, 1960, **1**, 36.
14. Reid, N. C. R. W., Hackett, R. M., Welbourn, R. B. *ibid.* 1961, **2**, 119.
15. Kammerer, W. H., Freiberger, R. H., Rivelis, A. L. *Arthr. and Rheum.* 1958, **1**, 122.
16. Work for Prisoners: report of the Advisory Council on the Employment of Prisoners. H.M. Stationery Office. 1961. Pp. 42. 2*s*. 6*d*.

that work is a most valuable part of a prisoner's training (there are grounds, it might have added, for believing that it is *the* most valuable part), and that the considerable prison labour force should not be wasted. The Council refuses to regard work merely as "punishment" or as a means of keeping the prisoner out of mischief. But it rightly adds that a half-hearted approach is of little use, and it insists on the need for competitive efficiency and for real-life conditions of work. Production-line work has special advantages and need not trespass on contracts carried out in sheltered workshops, even if the amount of prison work were quadrupled—as it should be. Nor need this increase affect employment outside, representing as it does only 0·06% of the work of the total working population of the country. Tailoring, woodwork, and engineering industries—and weaving in textile areas—find most favour with the Council.

It is unfortunate that the Council has not yet considered extramural work; for it may be in such endeavours as land, coast-line, or waterway reclamation that the best and healthiest creative labour will be found —and the least objectionable to trade unions. The Council has timidly recommended that earnings remain "pocket-money", though with a maximum of 10*s*. a week instead of the present 6*s*. It would have accorded better with its down-to-earth attitude to the nature of the industries to have called for realistic wages with appropriate deduction for lodging, families, tax, and National Insurance. In a parliamentary debate Mr. DAVID JAMES described such an increase as "grossly and totally inadequate", but the joint under-secretary of State for the Home Department ruled out full wages on the ground that prison industries could not foreseeably become sufficiently efficient and economic[17]—an odd objection in view of the Advisory Council's determination to make them so and the Home Secretary's acceptance of its opinions. Even though a prisoner's working day may never be as productive as that of the average workman elsewhere, the reward should roughly match the effort and the prisoner should see his earnings distributed justly—not only to his own pocket but to those to whom he is indebted. In this way some reparation to injured parties may become possible.

That other countries order these things better is well known—Denmark especially, which Mr. JAMES in the same debate put about a quarter of a century ahead of us. It is good therefore to have a clear account of the Danish penal scene from Dr. JAMES MCWHINNIE.[18] Denmark (which introduced free old-age pensions in 1891 and abolished corporal and capital punishment in 1933) has a more realistic system of employment and of incentives —both positive, in the form of earnings up to 50*s*. a week (half saved and half for spending), and negative—notably indeterminate detention of psychopaths. A ratio of prison personnel of 2 or 3 to 1 (1 to 1 in closed institutions) is a great help; and MCWHINNIE shows the way in which our services, judging by the Ingleby and Younghusband reports and the centres planned for psychopaths, are likely to follow the Danish model. It might be a good idea, too, to look more closely at the way Denmark runs prisons for juveniles and aftercare and penal work camps—for land reclamation, for example. In a thought-provoking final passage MCWHINNIE concludes: "Danish society seems to show relatively little aggression towards the criminal and it may be a reflection of this that in Denmark there is little aggressive crime."

17. *Hansard*, Aug. 4, 1961, col. 1802 et seq. See *Lancet*, Aug. 12, 1961, p. 378.
18. Denmark: a New Look at Crime. By JAMES B. MCWHINNIE. Published by the Institute for the Study and Treatment of Delinquency, London. Pp. 24. 2*s*.

Annotations

GRANTS—AND DONORS

THE Fleming Memorial Fund for Medical Research, which was launched only in March,[1] is making an early start with its constructive work; and its first grants will be considered by the trustees before the end of the year. The Fund exists to commemorate Sir Alexander Fleming, and the discovery of penicillin, by assisting basic medical research anywhere in the world; and its help will be given by grants either to institutions or to individuals or by way of national and international fellowships. With this aim, and with trustees and advisers well qualified to realise it, the Fund will be an invaluable addition to the independent Foundations whose joint function is to reduce the number of good ideas lost through lack of timely aid. But unfortunately basic research, and its promotion, often require a great deal of money, spent long before the results can be predicted; and unfortunately, too, expenditure which is not spectacular can appeal only to people with knowledge or imagination. The Fleming Memorial Fund really ought to have ten times as much as the £350,000 which (including covenants) has so far been subscribed; and at this stage it obviously needs the advocacy (even more than the contributions) of members of our profession, who should know better than anyone else the importance of the donor who does not demand quick returns. When one thinks of the number of people who have been helped by penicillin, an appeal to help further work, in the name of its discoverers, deserves a more general and generous response than it has yet had.

Copies of the Fund's appeal may be had from 26, Upper Brook Street, London, W.1; and applications for grants may be sent to the secretary of the trustees at the same address, on or after Oct. 1.

CRIMINAL STATISTICS

THE figures published for 1960 by the Home Office[2] show a continued rise in recorded crime—by 10% for indictable offence from 1959. True to form, murder (unchanged at 153) does not follow the general trend. It is perhaps an indication of our culture and of earlier maturation that unlawful sexual intercourse with girls under 16 jumped by 450 to 3608. Abortion came to light rather more often (221 in the year, an increase of about 70). The bulk of the increase was in crimes of all kinds against property and in wounding. Successful suicide, from coroners' returns, went down from 5236 to 5119. Non-indictable offenders, dealt with summarily, although over a million, were slightly down on the previous year.

1. *Lancet*, 1961, i, 597.,
2. Criminal Statistics, England and Wales, 1960. Comnd 1437. H.M. Stationery Office, 1961. Pp. 98. 8*s*.

The police solved some 30,000 more offences than in 1959 and just about kept up with the rise in crime—as before, about 44% of offences were cleared up. Only 10 of the 153 murders and 3 of 210 attempted murders remained unsolved during the year. Only 42 of 147 persons prosecuted for murder were so convicted (about half the average conviction-rate of all indictable offences), but 60 were convicted of a less serious crime. Manslaughter, too (106 out of 108 cases), was readily cleared up, and only 5 of the 470 people who caused death by dangerous driving got away. Wounding and assault are cleared up in about 5 cases out of 6. It is with offences against property that a betting man might take to crime; for example, of 41,000 cases of housebreaking only 14,000 were cleared up, and under 4000 people were actually found guilty. Non-indictable offences were more likely to bring conviction; of 912,535 people proceeded against, 871,730 were found guilty. 60% of all offenders were motorists. The next commonest offence—larceny—accounted for only 9·3%. By age, both sexes showed by far the biggest jump in crime in the 17–21-year group (12% and 21% for lads and girls respectively). Increase of crime in this age-group was related especially to larceny, fraud, and sex.

In sentencing, magistrates' courts have since 1938 used probation for indictable offenders less and less at all ages, and fines more and more; whereas higher courts have used probation at a consistent and far higher level—especially, of course, for under-21s. Fines they still use sparingly (10% for the 17-21s against the magistrates' 53%).

Those who talk of the moral decay of an affluent nation will find plenty of material in these indices of our social health; and yet, as Prof. Leon Radzinowicz pointed out the other day,[3] London remains one of the most law-abiding cities in the world. (Chicago, with a population of some 6 million, had 330 murders in 1959 [4]—more than twice as many as in the whole of England and Wales.) Moreover national statistics may be heavily influenced by marginal fluctuations in the habits of the police divisions and by changes in the public's readiness to report offences.

RESPIRATORY SYNCYTIAL VIRUS

IN the past few years many new respiratory viruses have been isolated,[5 6] but it has been slow work elucidating their relation to disease. Progress has been particularly slow in the more severe lower-respiratory illnesses of children—for example, bronchiolitis and pneumonia. At first it was hoped that the discovery of the adenoviruses had revealed the cause of much serious respiratory disease; but, except in certain special communities such as the Services and schools,[7 8] these viruses have not seemed to be important causes of respiratory disease in civilian populations. On the other hand Parker et al.[9] in Canada have found a relatively high incidence of severe disease in children due to adenovirus type 3. In 1956 myxovirus parainfluenzæ type 2 was implicated in outbreaks of croup in Toronto [10] and Cincinnati,[11] and since then cases due to types 1 and 3 have been described. In 1957 Liu [12] showed that Eaton's agent of primary atypical pneumonia could be effectively studied by the fluorescent-antibody technique; and Chanock et al.[13] found that it is an important cause of pneumonia, at least in military recruits.

There still remained much severe lower-respiratory infection of childhood for which no viral cause had been established (some is due to myxovirus parainfluenzæ 1, 2, or 3 and possibly also to the Salisbury cold viruses [14]). It now appears that respiratory syncytial virus, first isolated as chimpanzee coryza agent by Morris et al.,[15] is an important cause of bronchiolitis and pneumonia in infancy. It has been found to cause a significant number of cases in Chicago,[16] Baltimore,[17] Washington,[17] Philadelphia,[18] and Los Angeles.[19] Dr. Peacock and Dr. Clarke report in this issue (p. 466) preliminary studies which suggest that respiratory syncytial virus is also active in this country. This virus has proved difficult to work with, but Beem et al.[16] greatly improved the isolation-rate by using samples immediately for inoculation, without prior storage; they found that freezing and thawing destroyed the virus. Chanock et al.[17] also had much greater success with fresh specimens. Hamparian et al.,[20] on the other hand, found that virus survived a year's storage at −70°C. They believe that their technique of taking swabs in veal infusion broth rather than Hanks' solution, and storing them at −70°C in glass-sealed ampoules proof against seepage by carbon dioxide, explains their success. Hamparian and Sweet [21] introduced a better method of detecting the cytopathic effect of the virus by the addition of neutral-red, which stains the syncytia brightly.

In a series of cases of respiratory-syncytial-virus infection Hamparian et al.[20] isolated this virus from 62% and made a diagnosis by complement-fixation in 100%; whereas Chanock et al.[17] found a rise in complement-fixing antibodies in only 21 out of 34 cases yielding virus. The discrepancy was greatest in infants under 6 months, who are known to respond rather poorly to some other virus infections as measured by a complement-fixation test.[22] In Baltimore in the winter of 1959–60 respiratory syncytial virus was isolated from 16 out of 27 cases of bronchiolitis and 7 out of 13 cases of pneumonia in infants under 6 months—an isolation-rate of 57%. In Philadelphia it was responsible for about 38% of such cases in patients of all ages. Chanock et al.[17] note that in the winter of 1960–61 there was another outbreak of respiratory-syncytial-virus infection, again with a peak attack-rate in infants under 7 months, in which age-group it accounted for 37% of cases of bronchiolitis and pneumonia. The Bethesda workers [23] studied the response of

3. See *Lancet*, July 22, 1961, p. 202.
4. Uniform Crime Reports of the Department of Justice. Federal Bureau of Investigation: Crime Survey for 1959. U.S.A.
5. Huebner, R. J., Rowe, W. P., Chanock, R. M. *Ann. Rev. Microbiol.* 1958, **12**, 49.
6. *Lancet*, 1960, ii, 1338.
7. McDonald, J. C., Wilson, J. S., Thorburn, W. B., Holland, W. W., Andrews, B. E. *Brit. med. J.* 1958, ii, 721.
8. Kendall, E. J. C., Riddle, R. W., Tuck, H. A., Rodan, K. S., Andrews, B. E., McDonald, J. C. *ibid.* 1957, ii, 131.
9. Parker, W. L., Wilt, J. C., Stackiw, W. *Canad. J. publ. Hlth*, 1961, **52**, 246.
10. Beale, A. J., McLeod, D. L., Stackiw, W., Rhodes, A. J. *Brit. med. J.* 1958, i, 302.
11. Chanock, R. M. *J. exp. Med.* 1956, **104**, 155.
12. Liu, C. *ibid.* 1957, **106**, 455.
13. Chanock, R. M., Mufson, M. A., Bloom, H. H., James, W. D., Fox, H. H., Kingston, J. R. *J. Amer. med. Ass.* 1961, **175**, 213.
14. Tyrrell, D. A. J., Bynoe, M. L., Hitchcock, G., Pereira, H. G., Andrewes, C. H. *Lancet*, 1960, i, 235.
15. Morris, J. A., Blount, R. E., Savage, R. E. *Proc. Soc. exp. Biol., N.Y.* 1956, **92**, 544.
16. Beem, M., Wright, F. H., Hamre, O., Egerer, R., Oehme, M. *New Engl. J. Med.* 1960, **263**, 523.
17. Chanock, R. M., Kim, H. W., Vargosko, A. J., Deleva, A., Johnson, K. M., Cumming, C., Parrott, R. H. *J. Amer. med. Ass.* 1961, **176**, 647.
18. McClelland, L., Hilleman, M. R., Hamparian, V. V., Ketler, A., Reilly, C. M., Cornfield, D., Stokes, J. *New Engl. J. Med.* 1961, **264**, 1169.
19. Adams, J. M., Imagawa, D. T., Zike, K. *J. Amer. med. Ass.* 1961, **176**, 1037.
20. Hamparian, V. V., Ketler, A., Hilleman, M. R., Reilly, C. M., McClelland, L., Cornfield, D., Stokes, J. *Proc. Soc. exp. Biol., N.Y.* 1961, **106**, 717.
21. Cited by R. M. Chanock et al. (footnote 13).
22. Grist, N. R. *Scot. med. J.* 1957, **2**, 249.
23. Johnson, K. M., Chanock, R. M., Rifkind, D., Kravetz, H. M., Kugh, V. V. *J. Amer. med. Ass.* 1961, **176**, 663.

adult volunteers to this virus, and found that 20 out of 41 became febrile and another 13 gave laboratory evidence of virus infection. All these volunteers had pre-existing neutralising antibodies, which did not prevent infection though it may have mitigated it. These experiments were complicated by the discovery of SV40 (vacuolating virus)[24] in the respiratory syncytial virus used. SV40 was clearly not responsible for the symptoms, but its presence illustrates again the hazard of the use of monkey-kidney cells for diagnostic work. The position is further complicated by the discovery that the myxovirus SA19 [6 25] is a simian parainfluenza virus SV5.[26]

MAINTENANCE OF BLOOD-PRESSURE

NERVOUS control of the vascular system is important to all higher animals, and particularly to man owing to his vertical position. Some animals besides man can remain upright for an appreciable time—for instance, the circus dog that walks on its hind legs and the elephant that sits on a tub. The giraffe, with a head far above its heart, has its own problems, which it meets, at least partly, by a high systemic pressure.[27] By contrast, creatures such as the hutch rabbit die fairly quickly if held up by the ears—the wild rabbit is far more robust.

In man the rapid circulatory adjustments that enable him to move to and from the vertical position are subserved by the autonomic nervous system. With movement from horizontal to vertical, gravity causes blood to pool in the extremities; as a result the venous return to the heart is reduced, and tension or stretch receptors in the walls of the blood-vessels in and near the heart (notably on the right side) give rise to a reflex increase in heart-rate. Owing to the reduction in venous return the heart is filled less in a given time, and its size is therefore decreased and its output lessened. Consequently the aorta and carotid arteries are stretched less than before; and from baroreceptors or stretch receptors in the arterial walls fewer impulses travel centrally. The inhibitory influence on the vasomotor centre is reduced; and a greater outflow of sympathetic vasoconstrictor impulses travels to the blood-vessels below the heart level, so that the diameter of both arteries and veins is reduced. Thus less blood is sent to the legs via the arteries; less is pooled in the constricted veins; and more is made available for the upper half of the body, especially the intracranial structures. Narrowing of the veins reduces venous stasis, and so partly prevents loss of fluid to the interstitial spaces in the lower limbs—which, if unhindered, would lead to overt œdema.

On the efferent side of the adaptive mechanism circulatory adjustments depend on an increase (or decrease) in constrictor activity of the sympathetic nerves to the blood-vessels and alterations in cardiac rate and output. In conditions of increased constrictor activity—for instance, on assuming the vertical position—the nerve terminals on the smooth muscle of the blood-vessels transmit the impulses by liberating noradrenaline. In the upright position this substance is freed in amounts which increase its concentration in the blood and urine; and this concentration varies directly with the angle assumed by the body relative to the horizontal.[28] The stimulation of the sympathetic system includes stimulation of preganglionic fibres running to the adrenal medulla: here the chemotransmitter is acetylcholine, which on reaching the medullary cells induces release of adrenaline. This substance, too, reaches the blood and urine in recognisably increased quantities.

The net result, then, of assuming the upright position is arterial and venous constriction in the lower half of the body and an increase in pulse-rate. Owing to the considerable arterial constriction, the diastolic pressure rises and the cardiac output is reduced by some 20–25%.[29] Another result of standing is rapid reduction in the rate of urine flow, which depends on a reflex increase in the output of antidiuretic hormone. There is also retention of sodium owing to reflex liberation of aldosterone. These last two responses depend apparently on the change in venous return and in pulse-pressure.[30] Cerebral ischæmia leading to loss of consciousness can result from any event which causes a notable fall in blood-pressure—for instance, a precipitous fall in peripheral resistance or a fall in cardiac output, or both together—or from any factor (reflex, chemical, or physical) which disorganises central autonomic function.

In the healthy, when the upright position is maintained for a long time fainting may result from the activity of the sympathetic vasodilator supply to the voluntary-muscle blood-vessels. The splanchnic and renal beds also dilate. Vasodilatation in the muscle vessels immediately precedes the faint.[31] Why vasodilatation should occur after a period of apparently perfect adaptation is unknown. Owing to the widespread dilatation a large part of the total blood-volume is suddenly removed from effective circulation; and it is not surprising that the supply to the central nervous system is inadequate. Recovery is rapid if the patient is placed in the horizontal position. This form of syncope is especially likely to develop when the subject is warm and the skin vessels are dilated, either because of a high external temperature or because of previous exercise—that is, when the peripheral resistance is on the low side and the mechanism of blood-supply to the brain already under some strain. Emotional stress, pain, and fear profoundly affect the autonomic nervous system, and in some people induce fainting. The fainting of prolonged standing and stress seems to depend primarily on a decrease in peripheral resistance since it still occurs in the presence of atropine, which prevents bradycardia.[32]

The basically healthy may faint also during convalescence from an illness which has left the voluntary and involuntary muscles in a feeble state and the reflexes sluggish. The voluntary muscles of the lower limbs undoubtedly aid venous return; their contractions massage blood along the veins, in which the valves act as ratchets holding the blood in the new raised position. Another cause of fainting, more often related to emotional than to physical states, is hyperventilation.[33] Certain excitable patients overbreathe chronically. Under stress the respiration becomes even deeper. The chemical changes thereby induced add to the direct effects of emotion on the autonomic system, and syncope results. The chief chemical effect of hyperventilation is reduction in alveolar CO_2 tension and hence of the pCO_2 of blood, which in turn leads to cerebral vasoconstriction. Curing this type of syncope depends on resolving the patient's emotional tension—which is not always easy. Hyperventilation syncope sometimes has serious consequences. It is a habit of the young and healthy before high-diving or underwater-swimming to blow off as much carbon dioxide as possible, and thereby prolong submersion.

24. Sweet, B. H., Hilleman, M. R. *Proc. Soc. exp. Biol., N.Y.* 1960, **105**, 420.
25. Scultz, E. W., Habel, K. *J. Immunol.* 1959, **82**, 274.
26. Chanock, R. M., Johnson, K. M., Cook, M. K., Wong, D. C., Vargosko, A. *Amer. Rev. resp. Dis.* 1961, **83**, 125.
27. Goetz, R. H., Warren, J. V., Gauer, O. H., Patterson, J. L., Doyle, J. T., Keen, E. N., McGregor, M. *Circulation Res.* 1960, **8**, 1049.
28. See *Lancet*, 1959, ii, 332.
29. Bickelmann, A. G., Lippschutz, E. J., Brunjes, C. F. *Amer. J. Med.* 1961, **30**, 26.
30. *Lancet*, 1961, i, 207.
31. Barcroft, H., Edholm, O. G., McMichael, J., Sharpey-Schafer, S. *ibid.* 1944, i, 489.
32. Wayne, H. H. *Amer. J. Med.* 1961, **30**, 418.
33. See *Lancet*, 1959, i, 1278.

Usually this manœuvre does no harm; but occasionally death has resulted, presumably from syncope. Possibly respiratory and circulatory failure occurred because the oxygen used in exercise critically reduced the quantity reaching the brain, before the increase in pCO_2 had become unbearable and forced the swimmer to the surface.[34] Disaster is more likely to happen with fairly deep diving, because on rising from a region of high pulmonary alveolar pO_2 to the surface where this is less, the fall in tension may be great enough to prevent the venous blood from absorbing oxygen, and may even cause a movement of O_2 out of the blood and into the air in the lungs. The combination of extreme hypoxia with hypocapnia may well be fatal. By refraining from preliminary hyperventilation this state cannot be reached, since the pCO_2 causes sufficient distress to drive the swimmer to the surface. Hyperventilation before diving and underwater swimming should be strenuously discouraged.[35]

In the Stokes-Adam syndrome the fall in blood-pressure is due to a reduction in cardiac output rather than in peripheral resistance; it is commonest in the elderly, and heart-block is often detectable. Sometimes the cardiac output is reduced suddenly in patients with a hyperirritable carotid sinus; but in most cases the bradycardia is not so severe as to induce more than dizziness. Irritability of the carotid sinus may also lead to a reflex fall in peripheral resistance, with or without bradycardia. This condition can be differentiated from the Stokes-Adam syndrome in that pressure over the sinus will produce fainting and heart-block is unlikely to be present, though other types of circulatory disease may be found. Carotid-sinus irritability may give rise to vertigo, syncope, focal attacks, and mental changes.[36] Severe bradycardia and unconsciousness can follow irritation of vagally innervated viscera. The origin of the abnormal stimulus may be a tumour or inflammatory lesion; and even excessive gas in the stomach can, by pressure against the diaphragm, affect the heart—particularly in coronary-artery disease.[37] The stimulus may come from an instrument inserted into the œsophagus or the bronchi.[36] Obviously fainting may occur whenever the heart cannot meet the demands made on it—for instance, with valvular or coronary-artery disease, or with defects of the muscle or conducting system in the heart. Similarly, when the blood-vessels cannot respond appropriately, syncope may result. The vessel failure may be due to the rigidity of arteriosclerosis—either generalised or in a particular locality, perhaps in the nervous system.

Failures of wholly different origin are those due to administration of sympatholytic or ganglion-blocking drugs, and the unusual disorder known as orthostatic hypotension of unknown origin. In this last condition the failure of the sympathetic nervous system is such that the circulation cannot counteract the effects of gravity. The patient has no evident disability when recumbent, but movement to the vertical position is followed by inadequate or absent vasoconstriction in the lower half of the body, and the pulse-rate may not accelerate. The cause of this disabling condition is not clear, but it is commonly assumed to be due to spinal or peripheral lesions of the nervous system.[38] There are difficulties in accepting this explanation unreservedly, since in man and animals vascular tone returns after extensive sympathectomy and with it a remarkable degree of adaptability. Progressive orthostatic hypotension may, it seems, become manifest only in the presence of some factor besides interruption of peripheral sympathetic pathways. This factor may be humoral, but it does not seem to be an adrenal or pituitary hormone.[29]

34. Craig, A. B. *J. Amer. med. Ass.* 1961, **176**, 255.
35. *See Lancet*, Aug. 5, 1961, p. 304.
36. Hutchinson, E. C., Stock, J. P. P. *ibid.* 1960, ii, 445.
37. Morrison, L., Swalm, W. A. *J. Amer. med. Ass.* 1940, **114**, 217.
38. Wagner, H. M. *Bull. Johns Hopk. Hosp.* 1959, **105**, 322.

LEAD ENCEPHALOPATHY IN CHILDREN

LEAD-POISONING in children is apparently not uncommon in large cities in the United States [1]; in the Cook County Children's Hospital, Chicago, 142 such cases were treated in 1959,[2] and 42 of the patients had an encephalopathy. In the United Kingdom the disease is considerably less common, but the diagnosis is easily overlooked and should always be considered in obscure cases of apparent encephalitis or of raised intracranial pressure in childhood. In most cases the lead-poisoning results from eating plaster containing lead or flakes of lead paint (120 in the Chicago series), but the burning of old battery casings as fuel was the cause in 22 of the Chicago cases and was the cause also in the Rotherham outbreak in 1955.[3 4]

The cerebral disturbance in lead encephalopathy is due partly to cerebral œdema, and Greengard et al.[1] describe its treatment with intravenous urea. Lead encephalopathy is a serious and commonly fatal condition—nearly a quarter of the 42 cases in the Chicago series died. In general in the treatment of lead-poisoning the use of the chelating agent, calcium disodium edathamil, has proved effective; but in encephalopathy its effect is usually delayed, and cerebral symptoms may be exacerbated in the twenty-four to forty-eight hours after this treatment is started.[5] For this reason Greengard advises delaying the use of the chelating agent for twelve to twenty-four hours while more active measures to reduce the cerebral œdema are applied. Intravenous urea has been found valuable in reducing intracranial pressure in patients with cerebral tumours,[6] and Greengard has used it in 30 children with lead encephalopathy with encouraging results. He administered a 4% solution in 5% dextrose in a dosage of 1 g. per kg. body-weight by intravenous drip, and the course can be repeated each eight to twelve hours. It is, of course, necessary to establish that urinary secretion is adequate before starting this treatment, and the blood-urea should be estimated at intervals because levels above 75 mg. per 100 ml. are thought to be undesirable. It is difficult to draw precise conclusions from Greengard's figures, since additional methods of reducing intracranial pressure were applied in some cases, and the severity of the encephalopathy in the various cases is not clear; but the method seems logical and well worth further trial. The after-effects in children who survive lead encephalopathy may be serious, Cohen and Ahrens [7] reported on 17 cases; 3 died, 2 were not followed up, and 9 had moderate or severe residual symptoms.

Mr. A. M. A. MOORE has been elected master of the Society of Apothecaries of London.

1. See *Lancet*, 1959, i, 1189.
2. Greengard, J., Rowley, W., Elam, H., Perlstein, M. *New Engl. J. Med.* 1961, **264**, 1027.
3. Gillet, J. A. *Lancet*, 1955, i, 1118.
4. Travers, E., Rendle-Short, T. J., Harvey, C. C. *ibid.* 1956, ii, 113.
5. Smith, H. D. Cited by Greengard et al. (footnote 2).
6. Javid, M., Settlage, P. *J. Amer. med. Ass.* 1956, **160**, 943. Stubbs, J., Pennybacker, J. *Lancet*, 1960, i, 1094.
7. Cohen, G. J., Ahrens, W. E. *J. Pediat.* 1959, **54**, 271.

Special Articles

MANAGEMENT EFFICIENCY IN THE HEALTH SERVICE *

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IN this paper I put forward recommendations which include new methods of raising and distributing funds, and a new administrative structure for the National Health Service. The aim of the changes proposed is to assist those responsible for management in the National Health Service to fulfil their function—continuous provision of medical care of the highest quality that Britain can afford—which I believe the present structure tends to impede.

The processes of handling problems of management are analogous to those of handling medical problems. There is a body of knowledge of the general principles of management—its physiology and pathology—but any particular problem or case does require a systematic and detailed examination so that a diagnosis may be made. If a pathological state exists, then one must attempt to forecast the future, or give a prognosis. If recommendations for change (or treatment) are required, they must be communicated to the relevant persons in such a way that they are accepted, and appropriate action is taken.

Inherent Difficulties of Management in a National Health Service

In a health service provided free of direct charge, efficient management is particularly difficult because neither the purpose nor the " product " of the organisation can be clearly defined, and because there are few automatic checks to managerial incompetence.

Nebulous Nature of the Objective and " Product "

The objective of management should be to enhance the health of all the citizens, and the " product " should be the best medical care the nation can afford. But health and disease consist of innumerable heterogenous entities, and even their existence is often a matter of opinion. Furthermore, it is impossible to give a quantitative measure to the " product " of a hospital or other medical service except in crude terms.

In any large organisation management requires quantitative information if it is to be able to analyse a situation, make a decision, and know whether its actions have achieved the desired result. In commerce this quantitative information is supplied primarily in monetary terms. By using the simple, convenient, and measureable criterion of profit as both objective and product, management has a yardstick for assessing the quality of the organisation and the effectiveness of its own decisions.

Even outside a market economy (as in Russia) management of an organisation producing a homogeneous and therefore measurable product such as coal, wheat, or steel can estimate its efficiency by the volume of production per unit of work. Similarly in war, though the " product " of the Armed Forces is not measurable, the criterion of success—victory—is quite clear (perhaps deceptively so).

In a medical service, where the price system of a market economy tends to conflict with the aims of the service, and where the objectives and product are heterogeneous, and essential differences are qualitative, no simple measurements or criteria are available, except in exceptional and limited circumstances.

It therefore follows that the further top management is removed from the hospital, clinic, surgery, and the home, the less will it be able to know what is happening. If management does not know what is happening it cannot be efficient.

Lack of Automatic Checks

In the private sector of the economy there are two automatic checks to managerial incompetence—the necessity to make a profit, and the competition of other organisations. A private firm derives its income from the sale of its products, and if demand falls, or the products are unsuitable in quality or price, the declining receipts and profits will tend to put the firm out of business, or to make management mend its ways.

In a free health service there are of necessity no sales, and no profit-and-loss account. The income of the organisation continues whether the quality and efficiency of the service provided is excellent or poor. Furthermore, as the present health service is almost a monopoly, there is no ready means of comparison whereby the consumer can assess quality. Therefore indifferent management may continue undetected for years unless special checks are devised.

Principles of Management

The principles of management are well known:

1. Management should have an objective.
2. It requires information.
3. It should analyse complex situations.
4. It should make decisions involving action.
5. It requires authority to carry out its decisions, and should be responsible for them.
6. It should attract to its ranks people with ability and adequate training.
7. Management fulfils its function through the work of other people. It should therefore create an environment in which people can work well, it should ensure an adequate supply of equipment, it should build, maintain, and renew plant, and it should ensure an adequate flow of entrants to the organisation.

Defects in Management

Management in the N.H.S. has often been criticised, but it is not my purpose to repeat this in detail. I shall only indicate in general terms the ways in which the service fails to conform with the principles of effective management.

Distortion of Objectives

The objective of the service—the provision of the best care the nation can afford—has become distorted. Because it is difficult to obtain quantitative data indicating the *quality* of medical care provided, top management in a centralised health service is virtually unable to know whether or not this objective is being achieved. On the other hand, accurate measurements of the *cost* of the service are readily available to management. As there has been no careful and critical analysis of what the nation can afford, a decrease in expenditure of public money has appeared to be obviously desirable. Consequently, the objective of economy as an end-in-itself has dominated much managerial activity. The devastating long-term effect of this policy on the quality of medical care does not become apparent for many years, provided that when the policy is initiated there is a sizeable fund of high-quality material and human capital.

* Based on a memorandum submitted by request to the Minister's Advisory Council on Management Efficiency in the National Health Service, and to the Medical Services Review Committee.

Inadequacy of Information

In a very large organisation top management cannot function efficiently without quantitative data. With the prime objective of economy, the data collected in the N.H.S. have been mainly financial. General practitioners' prescriptions and the various activities of hospitals are carefully costed, with the aim of spot-lighting and preventing high expenditure.

Little attention has been given to the much more complex but important task of obtaining data to assess the quality of medical care provided. Even basic information about doctors, such as the rate of emigration, immigration, retirement, and entry into private practice and industry, are not continuously available. Without such data long-term planning in the Health Service is impossible.

Failure of Rational Analysis

Centralisation of managerial control gives those responsible for making decisions a task of immense complexity, because so many variable factors have to be taken into account, many of which cannot be quantified. The result has been major decisions which are arbitrary and irrational, such as the £400 million ceiling placed on N.H.S. expenditure in 1950, and the 5% cut in staff in all hospitals throughout the nation in 1953.

Decisions in a service subject to Parliamentary control aim at being acceptable rather than efficient. The Minister and his Department must try to make decisions which are acceptable both to the local bodies at the periphery and to Parliament. Members of Parliament may question any of the activities of management—however trivial—and the Minister has to give a satisfactory answer. These questions tend to direct the attention of the Department towards the tactical details which concern individual Members, and away from major strategic issues.

Lack of Action

With centralised control, the repercussions of any major decision are enormous and often painful. Consequently decision-making is avoided when possible. The most acceptable method of postponing a major decision is to set up a committee to make inquiries and seek further information.

The control of finance in particular is heavily centralised; but, as all decisions of any importance have financial implications, little managerial activity can occur at the periphery without approval from the centre. The length of the " chain of command " between periphery and centre, combined with the reluctance to take decisions, and the interest in economy, ensures that months or years elapse before decisions initiated at the periphery can actually be carried out.

Failure to Delegate

If management does not have authority to spend as it sees fit, then its authority is largely illusory. In the hospital service the authority to spend at an individual hospital goes back from the hospital to the hospital management committee, to the regional hospital board, to the Ministry, to the treasury, and finally to Parliament. A hospital management committee does have legal authority to spend, but largely as the superior bodies think fit, and so real authority is removed from the lower bodies.

If management does not have authority, then it cannot be held responsible for its activities; nor do its members feel responsible. The Act, by placing responsibility for every detail of the service in the hands of the Minister, drains it from the rest of the service, and tends to make it an irresponsible organisation. In actual practice many people at middle management level in the service act with a high degree of responsibility—but this is in spite of the administrative structure, not because of it.

Lack of Attraction to Competent Management

Efficient management of a modern hospital, or group of hospitals, is a highly complex task comparable to operating a steel mill or air-line. Members of boards and committees of management are unpaid, and part-time, often they know little about hospitals or management, and anyhow they are given little real authority. Under these conditions, it is difficult either to attract or hold those who can manage efficiently, although some outstanding individuals are still willing to serve in spite of them.

Huge sums of public money are spent by the boards and committees; but the financial rewards offered to their permanent officials, who should see that funds are used efficiently, are so small they have little attraction for the limited pool of managerial talent available to the nation.

Failure to Replenish

In the first seven years of the service, capital expenditure on the hospitals was only a third of what it had been before the war (when financed by charity and local authorities) at constant prices. The share of national income devoted to capital expenditure declined steadily between 1949 and 1957, and even the recent expansion has so far barely raised it to half the pre-war level.

The number of doctors in the N.H.S. has increased each year since 1948. The expansion was quite independent of the service and resulted from the low rate of retirement of doctors between 1948 and 1958—a delayed effect of the first world war—coinciding with the high rate of entry into medicine during and immediately after the second world war.

The increasing number of doctors has obscured the fundamental insecurity of the future supply. For the past ten years the number qualifying has declined steadily. The number of medical students in training in Britain is now almost back to the 1938 level, and is still falling. In the next five years the number of active doctors reaching the age of 65 will rise sharply. A shortage of doctors will soon overshadow all other problems of the health service.

Defects of Structure

The defects in management in the N.H.S. are symptoms which arise from its unsound basic structure. Attempts to remedy the symptoms can only be palliative and ineffective in the long run if the underlying pathology persists.

Centralisation

The National Health Service Act makes the Minister of Health responsible to Parliament for providing a health service for the nation. If he is responsible, then he and his department must have authority and power to exercise this responsibility. This inevitably tends to remove decision-making from the periphery and place it at the centre.

By the nature of the service, it is those at the periphery who usually know best what is happening; but authority has been transferred from them to those who can have little knowledge of the situation, nor of the results of the decisions they take. Although an individual Minister may attempt to delegate authority to peripheral bodies, a question in the House, an investigation by the Public Accounts Committee, or even the expectation of such an investigation, will tend to frustrate his efforts.

Method of Finance

The Act states that Parliament will supply money to the service according to need. As need is a relative concept, it

is meaningless to suggest that it alone can be used as a criterion for determining the total sum to be spent. In practice other criteria must be used, and they have been (1) a rigid cash ceiling, and (2) the pattern of spending of the preceding year.

Funds are supplied through the Treasury and consequently the service has been subject to the rules governing Treasury expenditure. As a result the service has been adapted to the method of finance, instead of the method of finance being designed to achieve the aims of the service. This is exemplified by the rule preventing unspent balances being carried forward after March 31, and the limitation of revenue expenditure to the precise purpose for which it is voted each year.

The Future

The administrative and financial structure of the N.H.S. is unsound. Nevertheless the only authoritative body which has investigated the service—the Guillebaud Committee—advised that no major changes should be made for many years, because none was required.

I believe that the course of events during the five years since the Guillebaud report was published indicate that the conclusions of the committee are in urgent need of revision. The service has undoubtedly " worked ", and superficially it may be considered a success. However, there is increasing evidence that this has been achieved by living on the material, human, and moral capital built up by past generations. These capital reserves are being consumed without being fully replenished, and as they become exhausted the service will deteriorate.

The coming shortage of doctors will strain the service considerably. The difficulty in staffing junior hospital posts is increasing, and nearly 40% are already filled by graduates from overseas. To keep the present establishment filled it will be necessary to rely on an expanding inflow of these doctors. Soon it will be difficult to replace all retiring consultants by adequately trained British specialists.

In the past year a severe shortage of new entrants to general practice has developed. The total number of doctors in general practice decreased between 1958 and 1959, for the first time since 1948, and the decline will continue for many years. Already the vacancies for principals cannot all be filled and the fall in the proportion of the population living in " under-doctored " areas has been reversed.

A falling number of doctors will impair their ability to provide the " middle class " standard of medical care that an increasingly prosperous population will expect. Consequently the demand for private medical care outside the service will rise. The provident societies already have a rapidly growing membership and income, and the British United Provident Association has set up a capital fund for financing new and modernised private nursing-homes to meet rising demand. But as the number of doctors in private practice increases, the shortage in the N.H.S. will be aggravated.

Once under way, a swing from the N.H.S. to private medical care financed by insurance could develop a powerful momentum. If it does, there will be ever increasing pressure by those using the private medical services to decrease expenditure of tax funds on a State service which they do not use. This will tend to produce more economy cuts and larger direct charges to patients using the State service—which in turn will increase the economic demand for private medical care.

With its present structure, the N.H.S. is unlikely to survive the coming difficulties as anything better than a second-rate service for the less prosperous. Perhaps, indeed, this is no longer preventable. However, I give below suggestions for change which could convert the service into a viable organisation and still be consistent with its ideals.

A New Health Service

A general plan is required, in the framework of which immediate practical steps can be taken.

Finance

Quantity of public funds.—Money will be voted for the service by Parliament as a proportion of national income to be reviewed every few years. The proportion will be initially about 4% of gross national product, which is roughly that spent on medical care over the past fifteen years. There will be no supplementary estimate (thus giving Parliament greater control over the volume of public expenditure), and money saved by economies will be used to improve the service, not to decrease its expenditure. This will divert attention away from economy as an end-in-itself, and make economy a means to building a fine health service—a more inspiring incentive than producing a cheaper one.

It is rational and realistic to determine the volume of health-service expenditure by using the criterion of national income, and not that of need. All prosperous nations spend a similar proportion of their national incomes on medical care, however it is financed. Because medical care is a stable " industry ", and the total need for it in a nation remains unaltered by advances in medicine, expenditure rises only a little faster than national income over many years.

Raising of public funds.—A special health-service tax will replace money derived from general taxation, National Insurance contributions, and the rates. This will be a tax proportional to income, paid in part by employer and in part by employee, with a similar levy on the self-employed and on unearned incomes. The individual citizen will then know how much he is paying for the service. Preferably, the health-service tax will be introduced as part of a comprehensive social-security tax. It will be paid into a health-service fund, independent of other Treasury funds.

Capital.—Capital works will be financed by the issue of health-service bonds, the interest and sinking-fund charges being borne by a portion of the income from the health-service tax specifically reserved for this purpose.

The replacement of obsolete plant should be a continuous process. It is perhaps forgotten now that one of the main arguments in favour of nationalising the hospitals put forward in the 1940s, was that the State alone could afford the huge investment programme required to remedy the deficiencies caused by inadequate pre-war finance, and the devastation of war. After thirteen years' experience of the present method of capital finance it is clear that it is even more ineffective in raising funds than the methods which it replaced.

Administration

Devolution of responsibility for detailed management, strengthening of central economic planning, and a clear distinction drawn between the two functions are essential. At present, with the Minister responsible for all aspects of the N.H.S., the Ministry is too involved in detailed work and the strategic issues and long-term planning are neglected.

National.—The Government will be responsible only for major policy within the service. This includes the size

of the health-service tax, the ratio of capital to current expenditure, the range of services to be supplied free of direct charges, and the scale of any charges which patients may be required to pay.

The Government will allocate money from the health-service fund to the regions. The basic criterion for assessing distribution will be the population covered, and eventually it will be the sole criterion. However, in the transition from the present system, some regions might suddenly be starved of funds and others flooded, because of existing inequities. Therefore in the early transition years distribution will be " loaded " to minimise violent changes, and the loading gradually reduced. Similarly if some regions are particularly short of plant and equipment they will initially have a higher share of capital than they would receive on the basis of population alone.

Regional.—Regional boards, covering areas comparable in size to the present regional hospital boards, will be responsible for major capital development, for the operation of the teaching hospitals, and for the organisation of such highly specialised services as neurosurgery and radiotherapy. They will distribute funds available for the current expenditure of the community health boards, using population as the basic criterion for allocation.

Community.—New boards—community health boards—will be responsible for the operation of all other hospital, domiciliary, and preventive medical services in areas with populations from 50,000 to 250,000 or so. They will integrate under one authority at the community level the three subdivisions of the health service, which are at present administered separately by hospital management committees, executive committees, and local authorities. The focal point of each community health service will be a comprehensive general hospital.

The community health boards will be free, within wide limits, to use money they receive to provide comprehensive medical care as they deem fit. They will have to account for how they have spent it, but they will not have to prove that they need it. They will be free to pay those in the health service as much, and in such a way, as they think appropriate; to run down services as they become redundant, and to introduce or expand others as the need arises; to use and borrow money for minor capital expenditure; and to build up cash reserves for future needs or emergencies.

Hospital.—A more effective method is required for the internal administration of hospitals than the present three separate systems of medical, nursing, and lay administration. As hospitals become increasingly complex organisations, the need for someone of equivalent status and authority to the managing director in industry becomes more obvious.

Appointment of Board Members

The Minister will appoint the members of the regional boards. The regional boards will appoint the majority of members of the community boards, but some will be elected locally to serve on them. All members will be paid, many will be full-time, and the number on each board will be strictly limited.

The community boards will be responsible, through the elected members, to the local citizens of the detailed management of the service—because it is the local population whom they serve. They will be responsible, through the appointed members, to the regional boards and the Minister for carrying out the general policy of the Government.

Quality Control

It is difficult for any organisation to know whether or not it is efficient and providing a service of quality to the community. In private industry the forces of the market tend to eliminate organisations which fall below a minimum standard. In a national health service, as this does not happen, special checks are required.

All boards will be obliged to request an impartial survey of their management efficiency, and of the quality of medical care they provide, every few years. Those conducting the survey will be independent of the health service—such as firms of management consultants, assisted by medical practitioners of eminence from other regions to provide the medical audit. The report will be presented both to the board concerned and to the immediate superior authority.

Research and Information

An important function of the Ministry of Health will be to collect and analyse data received from the boards, and to disseminate information to assist the boards in planning and management.

In addition a small permanent institute will be set up to study, analyse, criticise and recommend on the whole field of medical care, and health service and hospital administration. The institute will be related to a university, but independent of the Ministry of Health and of organised medicine.

Private Practice

Private practice has an important function in counteracting the defects inherent in a monopoly organisation. There is no necessary conflict between private and public medical practice, and they should be developed harmoniously. For instance, private beds will be provided in public hospitals, receipts will form a supplementary income for the hospital, and private practice related to them will be subject to the same medical audit as public practice.

Conclusion

If there is a long-term plan immediate steps can be taken towards implementing it. A commission should be set up at once to advise the Government on the future structure and finance of the National Health Service with a view to enacting new legislation. To assist it in its urgent task, the commission should be allocated funds to enable a firm of management consultants experienced in assignments of similar magnitude to report and advise on the overall structure.

Time is not on our side. The ideals of the health service are magnificent, but the mechanics of its operation are unsound. If the structure remains unaltered the great social experiment will fail.

BRITISH MEDICINE AND THE DEVELOPING COUNTRIES

A Commonwealth Medical Service?

A CONFERENCE held at the Royal College of Surgeons on July 27 was attended by about sixty people, representing universities, medical associations, research foundations, and Government Departments. Sir ARTHUR PORRITT, P.R.C.S., who presided, explained why the college had felt it necessary to call together representatives of the many bodies concerned with providing medical aid to the developing countries. Without some organisation to coordinate these interests and activities, there would be much frustration and wastage of money, man-power, and

ideas. Coordinated action was urgent, but it required the full and enthusiastic support of Governments, both in this country and in other parts of the Commonwealth. He hoped that, despite the present economic difficulties, this support would be backed by the provision of the substantial funds which would be needed. Urging the conference to think imaginatively, Sir Arthur suggested that they should have in mind as an ideal a " Commonwealth Medical Service ", which might include some underdeveloped countries outside the Commonwealth, and which would provide a free exchange of personnel at all levels, and a redeployment of medical man-power so as to assist those parts of the world which were desperately underdoctored.

Sir MILES CLIFFORD emphasised the desire of very many of the emerging countries, despite the growth of nationalist feeling, to seek medical help from this country in preference to any other. He believed it would be a tragic error if Great Britain were to turn its back on the opportunity to use its medical resources to the best purpose in assisting these countries. He stated as their principal needs: (1) advice of the type which used to be offered by the Colonial Medical Services; (2) personnel, very often at a basic level in terms of doctoring; (3) the influence of doctors from this country to help to fill the vacuum caused by the disappearance of the district officer and, to a growing extent, the teacher; and (4) a system of secondment and exchanges which would enable them, by being linked with the universities and medical schools of this country, to train their own future medical profession.

He paid tribute to the work of the Nuffield Foundation, and others, in sponsoring short-term visits which were of great value. He was confident that the medical foundations of this country and the Commonwealth would be glad to play their part in any scheme for providing coordinated assistance to the emerging countries.

In the subsequent discussion all speakers agreed on the urgent need for action, and for coordinated action, under some central organisation. There were various opinions as to whether this central organisation should be under the ægis of the Government, the universities, or the Royal Colleges. Other points made concerned:

1. The fact that, in many countries, what was wanted was preventive medicine, hygiene, nursing, and medical statistics, rather than specialist services.
2. The necessity for properly supervised postgraduate training in this country not only for the many students from overseas but also for a large number of our own young doctors.
3. The limited extent to which this country can at present provide surplus medical man-power to work abroad.
4. The teaching of potential teachers from countries overseas.
5. The great value of sending senior men for a number of years to give leadership and to take an active part in clinical medicine and surgery. In many countries such men would be more valuable, and more acceptable, than their juniors.
6. The need to select more carefully, and train more diligently, those who come to this country for postgraduate experience.
7. The risk that too much coordination might stifle individual enterprise and diversity of aid.

Mr. P. ROGERS, on behalf of the Government's new Department of Technical Cooperation, said that the Department would certainly require advice from the medical profession and would welcome the establishment, either under the ægis of the Department or independently of it, of a coordinating committee which could be consulted and could make plans.

Sir ARTHUR PORRITT, in summing up, suggested that a small working party should be set up to work out coordinating machinery. With the unanimous approval of the conference a committee was appointed to nominate the members.

THE WORKING PARTY

At a meeting of the nomination committee on Aug. 15 it was felt that the working party would need to stimulate a two-way traffic, encouraging doctors, teachers, and specialists to go to countries overseas, and facilitating arrangements for postgraduate students to come to this country for training. It would, moreover, have to ascertain the needs existing in overseas countries, and act as a centre of information. Its terms of reference were defined as follows:

To consider at a professional level the methods by which British medicine can contribute to the development of medical science and the medical services in the developing countries.

The countries to be considered at the present time would be Africa, the Middle East, and the Far East with the exception of Japan and China. Future consideration would be given to the countries of Latin-America.

The committee thought that, though the Department of Technical Cooperation would certainly require advice from the medical profession and would be setting up its own medical panel, the working party must be an independent body. It must, however, have direct access to the Minister of Technical Cooperation and the Minister of Health.

It was agreed that the working party should not consist of representatives of named institutions nor of individuals chosen solely for their suitability for the work, but rather of suitable individuals who could be regarded as representative of medical categories. Sir Arthur Porritt will be the chairman, and invitations have been sent to about fourteen others. Mr. Kennedy Cassels, secretary of the Royal College of Surgeons, will convene the meetings.

Points of View

MEDICINE AND HISTORY

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THE HISTORY OF MEDICINE

UNTIL the 19th century the history of medicine is largely a catalogue of the follies of medical mankind. For ages progress was stultified by the word of Authority. According to Robinson,[1] the Paris faculty, which was very powerful in medieval times, had a malign influence on the progress of medical science:

" Congenitally incapable of entertaining a new idea, it issued a decree in the 17th century that none may deviate from Hippocrates and Galen upon pain of excommunication . . . (It) pursued with incredible malignity everyone who dared suggest that surgery was of equal rank with regular medicine; it expelled, with bitter rancour, any member who prescribed the new drugs, such as antimony, cinchona and ipecac . . .; not only did it forbid Harvey's demonstration of the circulation of the blood to be taught, but it opposed Pecquet's discovery of the thoracic duct, and denounced Aselli's discovery of the lacteals."

Until Vesalius (1543) every anatomist saw a non-existent hole between the ventricles of the heart, because Galen had said that such a hole is present.

The few advances made before the 19th century were

1. Robinson, V. The Story of Medicine. New York, 1931.

chiefly in anatomy and physiology, such as the publication of *De Motu Cordis* by Harvey in 1628. The solitary substance which actually *cured* anything was cinchona bark, the active principle of which is quinine; and when it was introduced from South America in the 17th century orthodox physicians nevertheless refused to prescribe it, because it was unknown to Galen. With smallpox vaccination (which began at the end of the 18th century) and the discovery that scurvy could be prevented by fresh fruit and vegetables, the list of curative or preventive measures is almost complete. Otherwise, the only benefits, apart from consoling words, which physicians and apothecaries could give was relief of their patients' pain with opium and some other drugs. In addition, surgeons could do good in certain limited ways—e.g., by amputating gangrenous limbs or cutting for stone in the bladder—though at the cost of torturing the victims and at the risk of severe infection.

Nearly always the remedies advocated were harmful, repellent, or at best useless. In the London pharmacopœias of the 17th century the medicaments included the blood of the bat and the badger, the excreta of many animals, the skulls of malefactors hanged in the moonlight, bee glue, eel grease, viper's flesh, woodlice, and the saliva of a fasting man. In a popular 18th-century French dictionary of drugs we read that "fresh urine, 2 or 3 glasses drunk in the morning fasting, is good against gout, hysterical vapours, and obstructions. It may also be applied externally in gout and in skin complaints. Excrement of man can be applied to anthrax, plague bubos, and quinsies. Dried and powdered, it is recommended in epilepsy and intermittent fevers. Dose, one scruple to one drachm".

Although the immediate reason why individual physicians prescribed these disgusting and fantastic remedies was the voice of Authority, how did they arise in the first place? The main explanation appears to be the universal human habit of a-priori speculation—a habit which was especially prevalent in the Dark and Middle Ages. Having once decided, on theoretical grounds, that a remedy must work, the physician could usually confirm that it *did* work by the observation that the patient recovered; for the vast majority of human maladies get better, not from anything done by the doctor, but by the *vis medicatrix naturæ*. In addition, some remedies presumably worked because of their suggestive effect, and others because they stimulated or shook the patient.

In ancient and medieval times there were schools of medical men who called themselves empirics. They opposed the theorising of their times, and claimed that they gave remedies because they had proved them to be effective. Their remedies were probably just as useless as (though perhaps less harmful than) those of the orthodox; but the fact that they were attacked *because* they distrusted theory and instead performed experiments is a striking condemnation of the old orthodoxy.

In recent years empiricism in therapeutics has emerged triumphant, a characteristic example being the controlled therapeutic trial. Even traditional remedies such as rest and various diets are no longer accepted uncritically by the entire medical profession; the experiment has been tried of not treating patients for long periods in bed or of not giving them certain kinds of diet and then comparing their progress with that of the other patients treated along conventional lines. Yet care is taken not to describe this approach as empirical; for empiricism continues to be a dirty word in medical circles, though in other circles—the political, for example—it is a word of praise.

The first great advances in the basic medical sciences of physiology, histology, pathology, and bacteriology were made in the 19th century, and these were related to the advances in physics and chemistry. Careful clinical observation, aided by various new instruments and, at the end of the century X-rays, made possible great improvement in diagnosis. Anæsthetics and antisepsis enabled surgeons to perform more and more complicated operations. Preventive medicine had spectacular triumphs in the provision of proper drainage and clean water, and to a less extent by diminishing adulteration and infection in food. But in medical treatment there were no appreciable advances except in the abandonment of positively harmful procedures of the past, such as bleeding, starving, and blistering. At the beginning of the 20th century the physician was almost as helpless to influence the course of diseases (except malaria) as were Hippocrates or Galen.

In the first third of the 20th century several important therapeutic advances were made, such as the arsenicals in treating syphilis and some tropical infections, insulin, liver extract, and the powerful mercurial diuretics. But it was only after the introduction of the sulphonamides in 1935, and the antibiotics, beginning with penicillin in 1941, that curative medicine made much impact on the vital statistics.

MEDICINE IN HISTORY

Until recent times devastating plagues and famines were the habitual lot of mankind, and these had important effects on the course of history. In the Black Death, which invaded Britain in 1348, a third to a half of the population were said to have died. We are told that this disaster

> "precipitated the class struggle, and embittered the process of emancipating the villein . . . the market value of labour had been doubled at a stroke . . . the labourer who was already free struck for higher wages, while the villein whose labour was not free struggled against the legal demands of the bailiff for customary services . . . gradually he was led on to demand his full freedom . . ." [2]

In all campaigns before the 20th century more—usually far more—combatants died of disease than in battle. The course of a campaign was therefore often decided more by the chance of an epidemic than by the skill of the generals or the fighting ability of the soldiers.

What is surprising is that historians seem so ready to believe that, even before the 19th century, medicine significantly affected the course of disease. Thus Williams, on the 18th century, says: "From poor beginnings this age (1714–1760) shows a remarkable advance in both the theory and practice of medicine and surgery",[3] and Trevelyan writes:

> "The unexampled rise in population from 1760 onwards was due, not so much to earlier marriages and an increase in the crude birth-rate, though these had a considerable part in the affair before 1790, as to the saving of life by improvements in medical science and practice, and to an improved standard of living. . . . The disappearance of the Plague so long endemic on the island; the control of the ravages of scurvy and ultimately of smallpox; the reduction of ague and fever by the draining of the land; the advance of habits of cleanliness and the use of cheap cotton shirts; improvements in sanitation in London and elsewhere . . .; and above all else, more and better hospitals and better medical care of mothers and infants which greatly reduced mortality at childbirth or by 'convulsions',

2. Trevelyan, G. M. History of England. London, 1945.
3. Williams, B. The Whig Supremacy (vol. XI of the Oxford History of England). London, 1939.

rickets and other infantile diseases, all these were features of the 18th and early 19th centuries." [2]

To this I would reply that no measures which could be considered " medical science and practice " (with the possible exception of " ague bark " containing quinine) could have had any effect in causing the rise of population in the 18th century. (Smallpox vaccination did not come into general use till the 19th century.) In so far as the patients who were admitted to the hospitals were starving they were no doubt benefited. But in so far as they received the results of the " medical science and practice " of the time—the bleeding, purging, blistering, and the rest—their prospects of recovery were worsened, not improved. By far the most important cause of death in childbirth was puerperal fever, and probably women admitted to lying-in hospitals were more, not less, likely to develop this disease. The death-rate in these hospitals often exceeded 2%, and at times approached the awful figure of 10%.

THE ILLNESSES AND DEATHS OF INDIVIDUALS

Even today, with all the resources of the pathological laboratory and the X-ray department, and a necropsy if the patient dies, the nature of some illnesses remains obscure. And the " cause " of illnesses is often far more obscure than their nature: even when we can supply a partial reason—as when we say that a stroke has developed because the patient's blood-pressure is high—we may still be left with another unanswerable question, " Why is the blood-pressure high ?" In the past all these difficulties were far greater. Looking back, we may sometimes be able to hazard a guess at the nature of some historical personage's illness, but in the great majority of cases we cannot possibly know its " cause ".

Yet we habitually read in sober historical works confident statements about the cause of the illness or deaths of great men, such as the following from the *Dictionary of National Biography:*

" That night Henry (the Second) bade his vice-chancellor read him the list of traitors whose names Philip had given him. The first name was that of John. ' Enough,' murmured the King as he turned his face to the wall; ' now let things go as they may: I care no more for myself or for the world.' For 2 days he lay tossing in anguish and delirium, cursing his son and himself, muttering ' shame, shame on a conquered king ' till the approach of death."

" In the strongest man there is only a limited power of endurance. If he puts the work of 80 years into 40 years there can be but one result. So it was with the Prince (Albert, the Prince Consort). During the 3 or 4 last years of his life signs were not wanting, in recurring attacks of illness, that he was using up his physical resources too rapidly . . . His old friend Stockmar had said many years before that any severe illness would kill him. The prediction proved true. Early in November 1861 the Prince showed signs of serious indisposition . . . From (November 30) onward the Prince grew steadily worse. Typhoid fever was developed, and by the night of December 14, 1861, his strength had run down, and calmly and gently his noble spirit was released from its burden of ' world-wearied flesh '."

Such explanations, though more sober, are no more reliable than the ones given in *1066 and all that:* [4]

" Richard I . . . died soon after of a surfeit of saladins, and was therefore known in the East as Richard Cœur de Laitue."

" The younger Pitt (Balham) rose slowly to his feet and, pointing at Fox, exclaimed: ' Roll up that chap: he will not be wanted these ten years '. Having thus made his most memorable saying, Pitt was carried out of the House and died almost immediately of a surfeit of austerlitz."

4. Sellar, W. C., Yeatman, R. J. 1066 and All That. London, 1930.

History would be truer if the only causes of death stated were those of such people as Charles I and Edward II.

In particular, the repeated assertion that death or bodily illness are due to strain, responsibility, hard work, or sorrow usually rests on no evidence whatever, except when they were followed by suicide. Prime Ministers carry an exceptionally heavy burden of responsibility. Yet, of the Prime Ministers of the last hundred years, Palmerston, Russell, Gladstone, Rosebery, Balfour, and Churchill all achieved the age of 80 and Attlee is approaching this figure. Of the remainder who have died, all passed 70 except Bonar Law, who died of cancer, which is not one of the conditions attributed to strain. Their failure to die young can—and no doubt often has—been attributed to a " strong constitution ", but this is a mere ad hoc proposition; the reason for concluding that their constitutions were strong is that they lived to old age.

Robinson points out that aboriginal man could not grasp the conception of natural death:

" Disturbance or stoppage of physical life was due to supernatural causes—to the wrath of the dead, the uncanny powers of human enemies, the revenge of offended spirits. Terrifying as were the crocodile and hyena, he could see them and understand them and cope with them, but against witchcraft he had no weapon. Disease-demons were more numerous than the leaves of the forest, and they pursued him every moment of the day and night. He could escape the long serpent that awaited him, but not the ghosts and their magic." [1]

Perhaps we are not so different from aboriginal man as is generally thought. Although we no longer believe that illnesses are caused by evil spirits, there is still a widespread insistence to discover an explanation of illness and death; they are not thought to be natural. If the practising doctor says that the cause of someone's illness is unknown, a high proportion of patients and relatives refuse to accept this. Instead, they insist on attributing it to overwork, strain, or a " shock " (just as do historians) or to damp, draughts, or the menopause. And the medical profession tends to be less critical in ætiology than in other fields. Whereas treatment is as a rule analysed critically in books and articles, some disorders are now stated, on very slender evidence, to be " psychosomatic " or due to the " stress and strain of modern life ". Many of these same disorders were, in the recent past, attributed to constipation or to septic foci.

Symposium

VITAMIN B_{12}

FROM A CORRESPONDENT

AT the second European Symposium on Vitamin B_{12} and Intrinsic Factor, held in Hamburg between Aug. 2 and 5, nearly 200 experts discussed recent findings, some of which may influence the use of the vitamin in medicine.

The structure of a recently discovered vitamin-B_{12} coenzyme, which after many months of painstaking investigations at Oxford was elucidated just in time for Dr. DOROTHY HODGKIN to demonstrate it to the meeting, shows that vitamin B_{12} exists in the body largely as an unusually reactive coenzyme which is readily hydrolysed (e.g., by light) to yield hydroxocobalamin. Neither this nor the unhydrolysed coenzyme contains any cyanide (which of course is present in cyanocobalamin); and it seems probable that the pharmacopœial term " vitamin B_{12} ", at present restricted by spectroscopic tests to cyanocobalamin, will soon have to be extended to include also hydroxocobalamin. This latter form of vitamin B_{12} has a remarkable affinity for

cyanide, for which it is in fact a most effective antidote if administered in sufficiently large doses. At lower levels hydroxocobalamin may take up the traces of cyanide whose presence in certain conditions (e.g., tobacco amblyopia, demyelination) can produce undesirable effects. For the treatment of pernicious anæmia hydroxocobalamin appears to be equal in activity to cyanocobalamin and is better retained. Vitamin-B_{12} coenzyme does not seem to have any therapeutic advantage over cyanocobalamin or hydroxocobalamin.

The complex relation between vitamin B_{12} and folic acid is still far from being completely understood. In defective absorption of both folic acid and vitamin B_{12} the very low serum-vitamin-B_{12} levels may be considerably raised (though not to the normal range) by small doses of folic acid which completely remove other deficiency effects. On the other hand, in some patients with a subnormal serum-vitamin-B_{12} level administration of folic acid may still further reduce this level. Serum-iron may be high in untreated megaloblastic anæmia and reduced to normal after satisfactory therapy with folic acid or vitamin B_{12}.

In dietary deficiency of vitamin B_{12}, serum-iron has been found to fall with decreased intake of vitamin B_{12} and of animal protein in diets containing normal amounts of iron. This is thought to be due to ingestion of excessive amounts of phytate in wholemeal flour and bread. As the serum-vitamin-B_{12} level falls the severity of the deficiency effects in the peripheral and central nervous systems increases. Findings on British vegans and vegetarians consuming vegetable proteins fortified with vitamin B_{12} may help in the treatment of protein malnutrition in India, where the population is largely vegetarian and low serum-vitamin-B_{12} levels indicate dietary deficiency of the vitamin. An extra 2 million tons of protein needed annually in the Indian diet must be mainly vegetable protein and should be fortified with vitamin B_{12}.

Vitamin-B_{12} deficiency through lack of intrinsic factor (I.F.), as in pernicious anæmia, has stimulated efforts to purify and isolate I.F. The most potent preparations yet obtained are active in daily doses of 50 μg. or less and have very high binding capacity for vitamin B_{12} and its coenzymes which seems to be concentrated in one major peak observed in chromatography on DEAE cellulose followed by gradient elution. Care must be taken in the treatment of pernicious anæmia with oral preparations of vitamin B_{12} plus intrinsic factor, since resistance may gradually develop, after months or years, to hog intrinsic factor.

In parenteral treatment of pernicious anæmia 41 results in 19 patients showed a highly significant correlation between the logarithm of the amount of vitamin B_{12} retained in the body and the duration of its effect in days, when this effect was based on the maintenance of the serum-vitamin-B_{12} level within the normal range. Under these conditions the concept of a fixed daily need for vitamin B_{12} appears to be erroneous.

Medicine and the Law

Careless but not Liable

IN actions for negligence, it is not sufficient to show that there has been some failure to observe the required standard of care. The plaintiff must also have suffered harm, and that harm must be the result of the defendant's carelessness. The ramifications of this principle were illustrated by a recent case in which one Jones sued the Welsh Regional Hospital Board and a casualty officer for damages for alleged negligence resulting in the loss of an eye.

On the afternoon of June 8, 1956, Jones was using a hammer and punch in assembling the gears of some agricultural machinery when he felt something strike his eye. Finding his vision impaired, he went in a matter of minutes to the West Wales General Hospital at Carmarthen, where he was examined by the casualty officer. Finding a small corneal laceration on the right eye, she reported the case to a consultant ophthalmologist at another hospital. The ophthalmologist examined Jones the next morning and found that the eye was grossly infected in both the anterior and vitreous chambers. X-ray examination revealed a minute piece of metal in the vitreous chamber. The ophthalmologist immediately carried out a successful operation for the removal of the metal and gave instructions for remedial treatment by means of drops and ointment and the systemic administration of penicillin. Owing to some unexplained mishap there was no administration of penicillin systemically until the night of June 12–13. The infection did not respond to treatment, and on July 4 the eye was removed.

Jones alleged that the casualty officer was negligent in two respects: in not promptly communicating with the consultant, and in not taking a full and accurate history from himself. He also alleged that the hospital board was negligent in failing to carry out the consultant's instructions as to the administration of penicillin. There was no allegation of negligence against the consultant.

The learned judge dismissed both allegations of negligence against the casualty officer. She had in fact telephoned the consultant while the plaintiff was still in the casualty department. The plaintiff had not mentioned to her any sensation of pain or having felt a prick in the eye—which might have suggested to her that something had penetrated into one or other of the chambers. The casualty officer having made a proper report, it was entirely for the surgeon to decide when he would see the patient.

As regards the allegation against the hospital board, the learned judge said that the critical questions were, first, whether there was any real chance of the eye being saved after June 8; and, secondly, whether it could have been saved by penicillin.

Three medical witnesses for the defence said that in their experience they had never come across a case in which so seriously infected an eye had been saved and that, so far as they knew, there was no record of any such occurrence. They argued as a matter of theory that, even if there were any cases of such recovery, there was no case in which it could be shown that the recovery was due to the systemic administration of penicillin.

A medical witness for the plaintiff agreed that an infected vitreous was a very bad sign, but he did not regard it as necessarily involving the doom of the eye. He had tracked down two cases where it appeared that severe panophthalmitis had been cured by the administration of antibiotics. In one of them, which had been operated on only the previous week, determined antibiotic treatment had been followed by dramatic improvement in a severe infection of the vitreous. The witness admitted, however, that it was not possible to show at all affirmatively that it was the penicillin that brought about this improvement.

His Lordship was not prepared to hold that the experience in these two cases really broke down the case made by the defendants—that the eye was, according to every reasonable expectation, completely hopeless by June 9, and indeed by the previous evening when at the best it could have been seen by an ophthalmologist. He accordingly dismissed the claim against the hospital board.

His Lordship added that, had there been any reasonable prospect of recovery, he would have been faced with a very interesting and rather difficult point of law as to whether damages could have been claimed for the loss of a hope. He preferred to express no concluded opinion, but it seemed that as a matter of principle the loss of a hope should be the subject of damages. But it would have to be a measurable hope; if it were so remote that it could only be expressed by phrases such as " one in fifty or more " or " one in a hundred ", he would doubt whether that was sufficient proof of the existence of the hope to justify finding against a defendant.

In England Now

A Running Commentary by Peripatetic Correspondents

WHEN, in return for my application (10 copies), the Board sent a printed card regretting, as the postman pointed out sadly, that I had not been selected for interview, that seemed to be that. Odd, I thought later, when they started writing to my referees, and later still when they told me the date of the interview and to hold myself in readiness in case the committee wanted me to come along (proper rubbing salt in). A week after, a letter came addressed to me calling some quite different doctor to interview —a G.P., I expect, who had referred a patient and found himself with some surprise summoned to the regional H.Q. A few 'phone calls later another letter turned up with the right name but all the wrong degrees. On the Great Day to general astonishment the right committee turned up at the right place, and mostly at the right time; though the candidates were, by this time, expecting to find a group of perplexed omphalologists faced with a short-list of phenestrationists.

One must forgive a Board its staffing problems—especially at holiday times—but it was a bit galling after all that not to get the job.

* * *

What is a physiologist? An unrealistic fellow lost in academic waste-lands? The chap who has five months' holiday a year, goes home at four, and is expected to be a highly skilled technician at any surgeon's behest? To correct these ideas it is only necessary to look at the work of J. S. Haldane, born 100 years ago. While he was accumulating the basic data of breathing and blood-gas carriage, he was not only adding to academic knowledge, but publishing some of his lasting work in the journals of industry. In those days the distinction between the "pure" and the "applied" was not made so often as today. Ventilation defects of houses, sewers, ships, submarines, mines needed accurate gas-analysis, and though the analyser which he invented has been often "simplified" it has never been easily replaced. Recognition of CO as the lethal factor in mine after-damp opened up a whole aspect of blood-gas transport, and the CO-hæmoglobinometer of the clinician and the canaries outside the mine-manager's office were practical consequences. Divers' bends are still avoided by following the tables of times for ascent from deep waters worked out by Haldane and his colleagues some fifty years ago. Looking back, it is clear that the tables were based on some pretty heroic experiments, and it says much that they have needed little alteration. Concern with the anoxia which can hit the miner, the submariner, or the mountaineer led Haldane to expose himself to low oxygen-pressures in decompression chambers, to breathe O_2-poor mixtures to poison himself with CO; a more pleasant consequence was high altitude experiments with other physiologists on the mountains. The anæmia of the Cornish tin-miners was due to ankylostomiasis, not foul air, but the heat and discomfort Haldane experienced in the mines led him and his colleagues to work in humid heat to test the limits of their ability.

Haldane's method was to work out problems of industry on the spot or to bring them back into the laboratory, and to provide a solution which was a contribution to basic science and a practical aid to industry. The problems of laboratory, mines, factories, sewers, submarine-diving were all worked out as part of one relationship—working man with his work environment. J. S. Haldane's genius was a very practical English genius.

* * *

There is something unexpectedly homely in the report that Major Titov's first question, on returning from Space recently, concerned his wife's premedical examination results. Just a case of first things first? At any rate it was coming down to Earth with a vengeance. What we don't know is whether or not she passed, and from the silence on this point one can only assume the worst. (Khrushchev forgive me if I'm wrong). The stress of trying to describe the ovaries of the earthworm while one's dearest and not-so-nearest is orbiting away up there must be considerable, and to forget a few branches of the frog's aorta is surely pardonable under the circumstances.

* * *

After only two weeks in general practice my gratitude to mothers of feverish children who ring up for a visit with a ready-made offer of the diagnosis is still abounding. And that's not joking. The fevers course was always sketchy, and no-one ever touched on the really important stuff such as how to answer this sort of thing: "Well you see we're going off to Bournemouth in ten days' time and Johnny there hasn't had it and well you see Johnny's mother (that's my sister of course) is only six weeks' pregnant . . . and *will it be all right for Iris to go too, Doctor?*" After that one, calling for a swift return to the surgery ("Oh dear. Run out of prescription forms") and rapid consultation of the books, I made a point of doing a spot of homework beforehand, on the strength of the telephonic diagnosis. Which is why I felt pretty confident one morning to read on the message pad: "Please visit Master X, in bed with measles." Stuffed with revisionary facts I sailed along, to be met with a rather too well-looking child, slightly red-eyed. No Koplik's spots; but a conjunctivitis, and anyway the message had said measles, hadn't it?

"That's funny," said grandmother suspiciously. "Had them last year. Much iller he was."

"Whose diagnosis?" I managed to ask, as casually as a recent poleaxing allows.

She named a tremendous physicianly father-figure, who, though recently defunct, is still held in Æsculapian awe by the locals.

I breathed something about getting it twice sometimes. Grandmother now began to make little snorting noises, coupled with threatening movements towards the telephone and, presumably, the local executive council. I began to beat it fast, the old woman firing into my wake various subtle points in the differential diagnosis of the two measles.

Back home I rescrutinised the ill-fated message. It now read: "Please visit Master X, in bed with g. measles." That receptionist wants to watch her handwriting.

* * *

We go on developing bigger and better heart-lung machines and artificial kidneys, but has anyone paused to think what is going to happen in a hundred years? As limbs and organs age and grow useless, they will presumably be removed, until finally only the head remains. This will be attached to a white box which will perfuse it with old-fashioned blood, with appropriate additives to stop further ageing. As the number of these increases, they will be housed in huge "pre-tombs", where they will sit and watch television—in colour and 3-D, of course.

Occasionally their descendants will take them out for an airing and haircut. No doubt at such times a special treat will be laid on—one can imagine Lord's, with rows of heads sitting on their white boxes watching the Australians—sixes will be barred, of course.

Ancestor worship will have nothing on it.

* * *

A fellow correspondent [1] has complained about the tardiness of the Royal Air Force, which has only lately published its report for 1959 on the health of the R.A.F. The report on the health of the Army is now to appear in two parts—part I containing statistical tables and part II the main text. In part I of the latest report, which has just appeared, we are told that this new procedure "has been adopted in order to speed up the release of statistical information which is of topical value and interest." Yet the tables bear no stigma of hasty compilation—perhaps understandably as they deal with the year 1957.

1. *Lancet*, July 29, 1961, p. 262.

Letters to the Editor

EUTHANASIA

SIR,—As a young man I had the care of a number of patients dying miserably from tuberculosis. A little later I was for a time in charge of many cancer patients in a Home for the Dying—an unforgettable experience. In more recent years I have watched the ending of life in quite a few elderly friends and relatives—sometimes in dismal wards-for-the-chronic-sick, crowded with human wreckage—sometimes in still more dismal mental institutions.

All this experience leads me to agree heartily with your leader of Aug. 12 as to the " gross inadequacy of our provision for decent, seemly quitting of life, with relievable pain and distress relieved and comfort given ". And that summing-up is amply confirmed by Dr. Sheldon's recent report [1] on the grim conditions for the care of the aged in the Birmingham region. Dr. Exton-Smith's article [2] on how people died in the geriatric wards of a London hospital (where presumably all the resources of modern medicine were available to them) is also disturbing in that he found on several occasions that powerful analgesic drugs were totally, or partially, ineffective for the relief of severe pain; and that in patients with rheumatoid arthritis who had experienced severe pain over long periods (months to several years) narcotics had not been used for fear of habit-formation. It may also be noted in passing that 11 of the 220 patients repeatedly expressed the wish to die.

The suggestion at the end of your leader that we need a nation-wide drive for easier dying, analogous to that for safer childbirth, should certainly be considered, although it is perhaps overoptimistic to hope for an easy, even happy, death in " all but a few " in the foreseeable future. The recent work of Dr. Cicely Saunders, whose experience as a nurse and almoner and now as a doctor (and I should add one with a large gift of sympathy) makes it of exceptional value, might well give us a lead. I have visited her wards at St. Joseph's, Hackney, and have been much impressed by the atmosphere of contentment, even of cheerfulness, that Dr. Saunders and the devoted staff of Roman Catholic sisters have been able to create there. Their aim has been to make the patients fairly comfortable rather than to cure, and to that end they have relied not only on medical and nursing techniques, but also on a high standard of kindliness and the consolations of religion (when they were acceptable). It is perhaps open to question how far the latter could be utilised in general hospitals not staffed by groups of dedicated women, and among patients many of whom do not share their deep religious convictions. Nevertheless I personally should like to see an extension of the work at St. Joseph's.

In another part of your leader you refer to the doctor's part in euthanasia as " profoundly disturbing ". Everybody will agree; but is it ethically correct to be more concerned about the doctor's feelings than about the misery of his patient when incurable disease has made life for him a torment from which he longs to be set free? On a number of occasions in the past few years medical men have admitted that they have taken steps to cut short a patient's suffering, and even the Pope has declared that a doctor's first duty is to relieve suffering, even if by so doing the patient's life is shortened. The recent passing of the Suicide Bill (without a single dissentient voice!) brings us considerably nearer to a more robust attitude to this difficult problem. Can we doubt that within a short time, when the public realises that suicide is no longer regarded as a shameful act, many unhappy patients who see themselves going downhill to death after a few wretched days or weeks of pain and misery, will ask themselves: What is to be gained by " sticking it out " (and perhaps exhausting those who have the care of them)? How many of us doctors, if we knew ourselves to be dying—all too slowly—from an inoperable carcinoma of the throat, with daily increasing dysphagia and pain, and perhaps a terrifying sense of suffocation, would not come to the same decision as Dr. Charlotte Gillman, herself dying of cancer, when she wrote these memorable words:

" When all usefulness is over, when one is assured of an imminent and unavoidable death, it is the simplest of human rights to choose a quick and easy death in place of a slow and horrible one. Believing this choice to be of social service in promoting wider views on this question I have preferred chloroform to cancer."

Was that courageous decision any more dishonourable than that of Captain Oates, which has been widely approved? Dr. Gillman had the means to give effect to her decision—many of our patients have not. If we concede their right to be spared unnecessary suffering or distress should we refuse to help them to achieve it *when they ask for our help?*

Farnham Royal, Bucks. LEONARD COLEBROOK.

SIR,—Your excellent editorial draws attention to the inadequacy of our provision for decent, seemly death. What is quite clear in the pamphlet you criticise (" The Case for Voluntary Euthanasia ". Obtainable from the Euthanasia Society, 13, Prince of Wales Terrace, London, W.8) is that those who are most concerned with the problems of death and the dying have not been consulted. More than anyone else, general practitioners and nurses have frequent and intimate contact with dying patients. Yet of the fifty-seven people with whose approval the pamphlet is issued, not one is either a general practitioner or a nurse. The list includes twenty-one doctors, but more than half of these are laboratory workers. Of the rest, only four are practising clinicians, and three of these are plastic surgeons who presumably do not often treat dying patients.

But let us hope that both general practitioners and nurses will contribute to the ensuing discussion, both in your columns and elsewhere.

Dulwich, London, S.E.21. ANN MULLINS.

EXCRETION OF PORPHOBILINOGEN AND δ-AMINOLÆVULINIC ACID IN ACUTE PORPHYRIA

SIR,—I want to support the views expressed by Dr. Ackner and his colleagues.[1] Like them, I have been struck by the lack of correlation between the severity of the clinical symptoms in acute porphyria and the urinary level of porphyrins and their precursors, porphobilinogen (P.B.G.) and δ-aminolævulinic acid (A.L.A.); but I myself have not had the opportunity of studying this phenomenon more closely. I assume that Ackner et al. determined the levels of P.B.G. and A.L.A. in their patients daily over the periods specified in their table I, though this is not actually stated anywhere in the text.

1. Sheldon, J. H. Report to the Birmingham Regional Hospital Board on its Geriatric Services. 1961.
2. Exton-Smith, A. N. *Lancet*, Aug. 5, 1961, p. 305.

1. Ackner, B., Cooper, J. E., Gray, C. H., Kell M., Nicholson, D. C. *Lancet*, 1961, i, 1256.

The patient studied by Kelényi et al.[2] is especially interesting because the P.B.G. level was determined daily for three months; an excretion level of 136 mg. per twenty-four hours was reached in a latent period—a figure of the same order as that obtained in the seriously ill patients of Ackner et al. (their table II).

The analytical technique, ion-exchange chromatography on the resin Dowex 2-X8, 200–400 mesh, was introduced by Mauzerall and Granick[3] who give the apparent molar extinction coefficient of the P.B.G. Ehrlich reaction as $3{\cdot}6 \times 10^4$. The molecular weight of P.B.G. is 226 and the reading solution corresponds to a urine dilution of 1/20; and the concentration in the urine (c) in mg. per 100 ml. is calculated from the extinction (e), read in a 1 cm. cell, by the formula $c = 12{\cdot}6 \times e$. As the normal average P.B.G. excretion is about 0·1 mg. per 100 ml.[4] this means that the corresponding extinctions (readings in 1 cm. cells) are of the order of 0·008—very low indeed. We always read these weak solutions in 4 cm. cells to obtain maximum accuracy; and I believe it is of questionable value to perform a spectrophotometric reading if there is no visible red colour of the reading solution in a 4 cm. layer.

The resin itself may cause difficulties, because of bacterial growth, resulting in considerably lowered analytical values. But by simply washing the resin with distilled water, perfect function can be restored.

The nomenclature of the porphyrias is at present very confusing, and recent attempts to remedy this have not been successful. The proposals in Eales' review[5] are likely to increase the confusion; and they do not take into account the important work performed in eastern Europe, in particular that of Berman.[6] We still do not know enough to devise an entirely satisfactory nomenclature. We will have to collect not only clinical but chemical, enzymic, and genetic data on the porphyrias. The biochemists are at present busily engaged in collecting enzymic data; but clinicians are not yet aware of the need for more detailed chemical studies of both the patients and their relatives, including analysis of the fæces which now is often neglected. These studies are necessary for classifying a porphyria within the diagnostic system which is beginning to take shape.

A fundamental feature of all porphyrias is their tendency to latency. I have been much impressed by this in my studies of porphyria in pigs[7 8] and cattle.[8 9] In pigs, congenital porphyria is inherited as a dominant Mendelian factor like acute intermittent porphyria in man, whereas in cattle it is inherited as a recessive like most cases of congenital porphyria in man. We have found on several occasions that even severe congenital cases in pigs may "burn out" completely leaving no trace when the pigs are slaughtered at the age of six months. In cattle most cases are so slight that they are found only on close clinical and chemical study. This makes it likely that mild cases of congenital porphyria in man may be much commoner than is generally believed.

A curious finding is that, in pigs, photosensitivity is completely absent in porphyria, even in severe cases with high porphyrin levels in the blood, despite the white skin of Danish pigs. This is hard to explain on the supposition that the simple presence of porphyrins in the organism causes the photosensitivity. It suggests that the mechanism is more complicated.

The present fashion is to speak of two types of hereditary hepatic porphyria, the Swedish (common acute intermittent) and the South African (variegate porphyria); but, like Waldenström,[10] I think that the picture is more complicated, these two forms being only two alleles out of a series of many, originating by mutation of a single gene.[11] The myoporphyria of Vannotti may be a third form. The Swedish and South African forms have been traced to single sources some hundreds of years back. But new mutations are constantly taking place which may result in types which are not quite identical either clinically, chemically, or enzymically. We have found such mutations in Danish pigs.[7] We can distinguish new types arising in this way only by careful examination by all means at our disposal; this study has hardly begun. For acute porphyria the most important chemical tests are of two types: analysis (1) of urine for P.B.G., and, if possible, A.L.A. as well, and (2) of fæces, for coproporphyrin and protoporphyrin. Isolation of crystalline coproporphyrin ester to distinguish type I from type III may be useful. Enzymic studies would be more fundamental still, but also much more difficult to carry out.

A study of other abnormalities of metabolism has hitherto been neglected. Mellinkoff et al.[12] have recently found that the aminoacid pattern of the urine was definitely abnormal in 12 cases of acute porphyria. This is further emphasised by the findings in an often forgotten form of porphyria in which the main excretion product is coproporphyrin III, but where abnormal aminoacid patterns play an important role, especially in homozygotes.[13]

Acute intermittent porphyria has now been reported in practically all countries and races.[5] It has also been found in the isolated communities of the Faroe Islands[11] and Iceland.[14] The frequency may be high in the Central European countries as well as Northern Sweden because 2 of our 80 Danish cases are from countries in central Europe, 1 from Austria and 1 from Poland.

Svendborg, Denmark. TORBEN K. WITH.

PSYCHIATRIC ASPECTS OF ACUTE PORPHYRIA

SIR,—I reported a case of porphyria with endogenous depression, in which we had given electroconvulsive therapy[15] with good results.

My reply to Dr. Cashman[16] and to Dr. Ackner and Professor Gray[17] is that of course we did not induce anæsthesia with barbiturates. The man was given a small dose of atropine by mouth and 1·5 ml. gallamine triethiodide ('Flaxedil') intravenously only. This is our routine method of avoiding fractures during E.C.T. We have used it for more than ten years without complications. Sedatives have seldom been necessary.

University of Gothenburg Psychiatric Clinic,
Sahlgrenska sjukhuset,
Gothenburg, Sweden. M. B. HOLMBERG.

FŒTAL HÆMORRHAGE INTO THE MATERNAL CIRCULATION

SIR,—The main point of our "ghost story" (June 24) was to report the clinical application of a simple diagnostic method. If a fœto-maternal transfusion has occurred, examination of the mother's blood by Zipursky's or a similar technique shows fœtal erythrocytes against a background of maternal "ghost" cells.

In the case reported there was good evidence of placental trauma. Even without trauma, however, fœtal erythrocytes can penetrate into the maternal circulation; and, as Dr. Laurance and Dr. Leonard write (July 29), a significant fœto-maternal transfusion may occur with a normal delivery. Two such instances have been recognised in Bristol since our original report was written.

JOHN APLEY
I. D. FRASER.
Bristol Royal Hospital
for Sick Children.

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3. Mauzerall, D., Granick, S. *J. biol. Chem.* 1956, **219**, 435.
4. Haeger-Aronson, B. *Scand. J. clin. Lab. Invest.* 1960, suppl. 47.
5. Eales, L. *Annu. Rev. Med.* 1961, **12**, 251.
6. Berman, J. Porfyricka choroba; patofysiologie a klinika. [Porphyria; pathology and clinical aspects.] Prague, 1960.
7. With, T. K., Clausen, H., Højgaard-Olsen, N. J. *Beretn. Forsøgslab. Kbh.* 1959, no. 310, p. 40.
8. With, T. K. *Vet. Med., Praha*, 1960, **23**, 65.
9. Jørgensen, S. K. *Brit. vet. J.* 1961, **117**, 1, 61.
10. Waldenström, J. *Nord. med.* 1959, **62**, 1203.
11. With, T. K. *Ugeskr. Læg.* 1960, **122**, 63.
12. Mellinkoff, S. M., Halpern, R. M., Frankland, M., Geipel, M. *J. Lab. clin. Med.* 1959, **53**, 358.
13. Berger, H., Goldberg, A. *Brit. med. J.* 1955, ii, 85.
14. Torsteinsson, J. Personal communication.
15. Holmberg, M. B. *Lancet*, 1961, i, 1226.
16. Cashman, M. D. *ibid.* p. 1349.
17. Ackner, B., Gray, C. H. *ibid.* p. 1410.

PHRENOLOGY OF SCHIZOPHRENIA

SIR,—I strongly support Dr. McFie's plea (Aug. 12) for an English standardisation of psychological tests, a need to which I have myself drawn attention elsewhere.[1] I also heartily endorse his call for a refinement in the constituent subtests of psychological batteries, so that intellectual functions may be more precisely identified and these fundamental psychological functions eventually related to their neurophysiological bases; and we must always bear in mind that the latter develop, mature, and decay, and are no more static than the psychological functions which they subserve.

McFie also suggests that psychiatric states may reveal patterns of intellectual impairment similar to the specific deficits he has found associated with neurological lesions involving particular areas of the cerebral cortex. Following his original statistical study I suggested this possibility in relation to the symptomatology of schizophrenia[2]; and the accompanying table is an attempt to correlate psychological, neurological, and psychiatric phenomena in this way.

PATTERNS IN SCHIZOPHRENIA

Primary mental abilities of Thurstone[3]	Cortically localised abilities[4]	Schizophrenic symptoms
Verbal ability: Proverb test; verbal classification and relation	Left postcentral: Verbal intelligence and similarity "Semantic dysphasia"	Thought disorder
Verbal fluency: Word finding and making; anagrams	"Jargon dysphasia"	Verbigeration
Numerical ability: Arithmetical problems	Left parietal: Arithmetical subtests "Acalculia"	
Spatial ability: Tests of laterality with shape and pattern	Right parietal: Visual constructive test; Koh's blocks "Dyspraxia and Agnosia"	
Perceptual ability: Recognition of similarity in drawn and written patterns		Hallucinations
Inductive reasoning: Solution of codes, letter series and groups of letters	Right frontal: Picture arrangement to tell a story	Delusions
Memory: Recognition of drawn patterns and memory for learnt verbal and numerical associations	Size rather than site of neurological lesion responsible	Dementia præcox

The idea is to suggest the neurophysiological basis common to the three fields rather than to equate the phenomena in one field exactly with those in either of the others. Thought disorder may exhibit "stereotypy", for example, whereas dysphasia reveals "perseveration", but the distinction need not be relevant in the present context. Similarly hallucinations and perceptions are not the same, but probably derive from the same or closely related neurophysiological bases.

In the first column of the table, Thurstone's primary mental abilities are factors statistically extracted in the process of doing intelligence tests, as the elemental functions involved in various molecular admixtures in solving psychological problems, whatever their complexity or the speed demanded for their correct solution. Since, however, they are the outcome of analysis of existing intelligence tests, they may still be open to the refinement called for by McFie.

In the second column, I am tempted to insert "left frontal" in the space partly occupied by "jargon dysphasia", and the other blank spaces in the table provide food for thought and may make us examine schizophrenic patients again in a new light.

In the third column, the inclusion of the old term "dementia præcox" merely serves to draw attention to those patients whose abilities are widely affected, but who may none the less recover fully. In contrast we are all familiar with the schizophrenic patient who obviously knows his way about the hospital and knows to a remarkable extent what is going on around him, but who is unable to communicate clearly owing, it seems, mainly to disturbance of his language functions.

Similar patchy involvement of abilities can be seen in a series of patients with senile or other organic dementias. In schizophrenia both the patchiness and the reversibility of the process are understandable if we accept a vegetative nerve supply to the cortex, which may reveal innate functional anomalies such as are assumed to underlie some instances of conditions such as spastic colon and essential hypertension.

Ide Hill, Kent. J. P. CRAWFORD.

1. Crawford, J. P. *Post Grad. med. J.*, 1955, **31**, 180.
2. Crawford, J. P. Psychosynthesis. London. 1956.
3. Eysenck, H. J. Uses and Abuses of Psychology. London, 1953.
4. McFie, J., Piercy, M. F. *Brain*, 1952, **75**, 292.

CONVERSION OF ST. EBBA'S?

SIR,—Your annotation (Aug. 12) on the South West Metropolitan Board's proposal to convert St. Ebba's into a hospital for the mentally subnormal must augment the uncertainty felt by mental-hospital staffs since the Minister of Health's speech on March 9 at the annual conference of the National Association for Mental Health. Your report of the conference [1] commented on the "profound anxieties about the future of their staffs" aroused by the policy announcement, and similar anxiety has been expressed in Parliament [2] and in your columns.[3]

St. Ebba's appears to be amongst the first of the hospitals to be directly involved in the changes adumbrated by the Minister, and the senior medical staff committee would like to draw attention to the following:

In the House of Lords debate on the hospital services [2] Lord Taylor suggested that mental hospitals with 2000 or more beds could only be treated by a bulldozer. He went on to say that a hospital with about 800 beds could be "a true therapeutic community and a powerhouse of psychiatric good service". When the conversion of just such a hospital into an institution for adult subnormals comes apparently first in the planning programme it seems to us that some apprehension about the remainder of that programme is justified.

The Minister [2 3] has pointed out that more rather than fewer people may be required for the psychiatric services of the future. This is a welcome assurance in the long term but so far no hint has been given as to where or how these people will be employed. The short term is dominated by all too concretely immediate plans that will drastically reduce the psychiatric posts available. The staff of St. Ebba's could probably be distributed among other mental hospitals, but since half of these must presumably be earmarked for elimination the problem does not stop here. As the "doomed institutions" [1] have not been specified, the staff in all mental hospitals are left in a state of increasing uncertainty, with no idea as to their future role.

We would suggest that, difficult though it may be to make exact forecasts, the time has come for more detailed statements about the future of psychiatric services, and for discussion with those whose careers are so intimately involved in these plans.

St. Ebba's Hospital, Epsom, Surrey. E. F. CARR
Secretary, Senior Medical Staff Committee.

LANGUAGE: THE LOST TOOL OF LEARNING

SIR,—Dr. Sanchez (Aug. 12) asks "would you rather be treated by a doctor because he writes perfectly?" I believe that the very fact that a doctor takes the trouble to write clear English makes it probable that his *thinking* is clearer than that of a colleague who writes with the faults Sir George Pickering deplored.

Tonbridge, Kent. A. R. N. ROBERTS.

1. See *Lancet*, 1961, i, 608.
2. *ibid.* p. 996.
3. *ibid.* p. 1151.

NUCLEAR SEX IN TRIPLOID XXY HUMAN CELLS

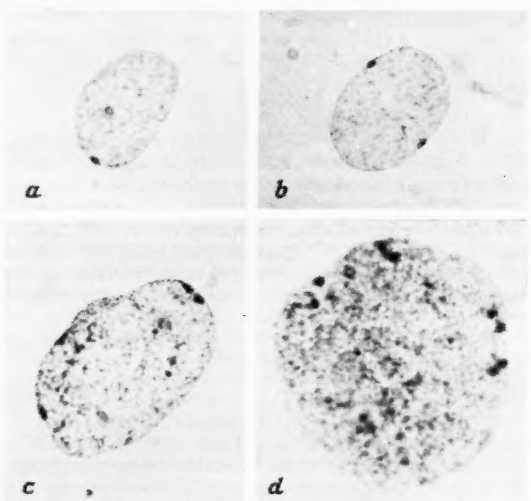
SIR,—In their interesting letter (Aug. 5) Professor Böök and Dr. Santesson produce evidence to support the suggestion that one set of autosomes may act as a "suppressor" for one X chromosome and that any X chromosomes in excess may produce a sex-chromatin body in the interphase nucleus.[1]

One can express this relationship between the number of sex-chromatin bodies (B) and the number of X chromosomes (x) by the following equation:

$$B = x - \frac{p}{2}$$

where p is the degree of ploidy of the cell. For diploid cells $\frac{p}{2} = 1$, and all recent observations agree that the number of sex-chromatin bodies is one less than the number of X chromosomes in diploid cells.[2]

Observations which I have made, using the technique of Ross,[3] on the sex chromatin of cells cultured from skin biopsy specimens support the hypothesis. The majority of cells derived from two cases of Klinefelter's syndrome having an



Four cells from the same culture in an individual with an XXXY sex-chromosome constitution: (*a*) diploid cell with 1 sex-chromatin body, (*b*) diploid cell with 2 sex-chromatin bodies, (*c*) presumed tetraploid with 4 sex-chromatin bodies, (*d*) presumed octaploid with 8 sex-chromatin bodies. (×800 app. all cells.)

The occurrence of the bodies in pairs is probably due to endoreduplication, which was known to have occurred in some cells in this culture.

XXXY sex-chromosome constitution were found to have 1 or 2 sex-chromatin bodies. However, some large cells had 4 bodies and even larger ones had 8 (see accompanying figure). In the chromosome preparations from the same cultures an unusually large number of polyploid cells was observed. Rough measurements of the surface areas of the flattened nuclei support the suggestion that the cells with 4 bodies are tetraploid and those with 8 bodies octaploid. The finding of 8 sex-chromatin bodies in an octaploid XXXY cell can be predicted from the above formula.

Our limited observations on normal male and normal female cultures agree with those of Reitalu [4] in that sex-chromatin bodies are not seen in the former though it is certain that a few polyploid cells are present, while an occasional cell with 2 sex-chromatin bodies is found in normal females.

The equation predicts approximately the sex-chromatin observations in cases with morphologically abnormal X chromosomes. For example, we can say, in a patient with one normal X chromosome and one deleted X chromosome,[5] that $x = 1{\cdot}6$. Therefore $B = 0{\cdot}6$, which in this case means that the sex-chromatin bodies are smaller than normal. (Since 0·6 of a chromosome is not really meaningful, x could be more accurately defined as the $\left(\frac{\text{length of X chromosome material}}{\text{length of a normal X chromosome}}\right)$. The use of the formula in this way assumes that the whole, or a large part, of the X chromosome is involved in the formation of sex chromatin.

If we now consider an XXY triploid, $B = 0{\cdot}5$; I am not at all certain how to interpret this. It seems reasonable, where there is a morphological abnormality of the X chromosome, to presume that a fraction represents a difference in size of the sex-chromatin body, but in a triploid where the X chromosomes are normal this will probably not be true. The presence or absence of sex chromatin in these cells will probably depend on whether an *additional* haploid set of autosomes can "suppress" the second X chromosome. Professor Böök's observations suggest that this is so. It would be interesting to know whether it is always so; sex-chromatin studies on other examples of triploidy would be most valuable.

I would like to thank Mr. A. Ross and Mr. J. Mitchell for their technical assistance.

M.R.C. Clinical Effects of Radiation Research Unit, Edinburgh.

D. G. HARNDEN.

TRIPLOID CELL CULTURES FROM A MACERATED FŒTUS

SIR,—In your issue of June 10 Professor Penrose and Mrs. Delhanty, in a very interesting paper, emphasised that "although the first accurate observations on normal human chromosomes (Tjio and Levan 1956) were made with cell cultures taken from fœtal tissues, the opportunities for investigating the chromosomes in cases of natural abortion have not so far been greatly exploited". This statement is, however, not completely correct. 33 years earlier (1928) Kemp was the first to count the number of chromosomes in human somatic cells in cultured tissue specimens, a method which has since been employed by several workers studying this problem.

Most of these workers arrived at approximately the same result. Kemp, on the basis of his investigations, regarded a diploid chromosome number of 48 as the most likely in man. He pointed out, however, that in most cases some doubt prevailed about one or two chromosomes, but that in general no counts differed more than 1 or 2 from 48. Kemp's analyses were published in Danish,[6] French,[7] and German [8]; and the value of this specific technique was emphasised by Hsu [9] and Elhmolt.[10]

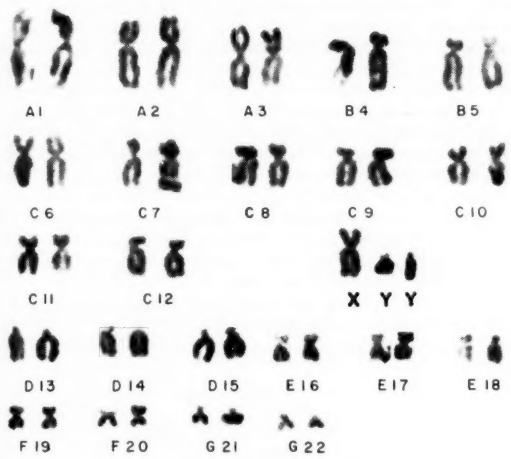
University Institute for Human Genetics, Copenhagen.

TAGE KEMP.

AN XYY HUMAN MALE

SIR,—Four abnormal sex-chromosome combinations may result from faulty separation of the sex-chromosomes during oogenesis and/or spermatogenesis: XO, XXY, XXX, and XYY. To date, only the first three conditions (and the rare XXXX, XXYY, and XXXXY) have been described and confirmed. We wish to present preliminary findings on a probable XYY male.

1. *Lancet*, 1960, ii, 191.
2. Stewart, J. S. S. *ibid.* 1960, i, 825.
3. Ross, A. *J. med. Lab. Tech.* 1960, **17**, 178.
4. Reitalu, J. *Acta genet. Med. Roma*, 1957, **6**, 393.
5. Jacobs, P. A., Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *Lancet*, 1960, i, 1213.
6. Kemp, T. *K. danske vidensk. Selsk.* 1929, **7**, 1.
7. Kemp, T. *C.R. Soc. Biol.* 1928, **99**, 1601.
8. Kemp, T. *Z. mikr.-anat. Forsch.* 1929, **16**, 1.
9. Hsu, T. C. *J. Hered.* 1952, **43**, 167.
10. Elmholt, L. *Acta path. microbiol. scand.* 1958, **43**, 241.



Karyotype of father.

A forty-four-year-old white man of average intelligence and without physical defects, despite the 47 chromosomes found in his marrow and blood, started work at seventeen after two years of high school. He has been married twice; 6 children (1 died at age 3 as a "blue baby") resulted from the first marriage, and 2 from the second. Each of his wives gave birth to at least one abnormal child. An eighteen-year-old daughter of the first marriage has had amenorrhœa, no breast development and, at operation, was found to have no internal sex organs. The nuclei of her buccal mucosa were chromatin-positive and her marrow cells were shown to have 46 chromosomes with a normal XX constitution. A twenty-two-month-old daughter from the second marriage is a typical 47-chromosome mongoloid. Also one miscarriage occurred in each marriage.

CHROMOSOME CONSTITUTION

Source of cells	Cells with chromosome number of				Total cells counted
	45	46	47	48	
Blood	0	3	37	1	41
Blood	0	1	26	2	29
Marrow	1	8	68	0	77

All other children are apparently living and well. Since they have been anonymously adopted we have not been able to study their chromosomes.

Their father claims to have normal libido, and results of examination were unremarkable. He has somewhat large facial features, is obese and weighs 287 lb., and has a neurodermatitis, an umbilical hernia, and, in the left mandible, has had a cystic lesion for many years. The buccal-mucosa cells were chromatin-negative.

His chromosome constitution was determined on three occasions. Two separate blood samples were cultured by the procedure of Moorhead et al.[1] and metaphases in freshly aspirated sternal and iliac crest marrow were analysed after performing the "direct squash" technique.[2] Nearly 90% of the metaphases contained 47 chromosomes (see accompanying table). In its arm ratio and size, the extra chromosome shown in the karyotype of the figure consistently resembles the Y more than the small autosomes G21 and 22, judged according to the criteria of the Human Chromosome Study Group.[3] Absence of the severe mental and physical stigmata regularly associated with autosomal trisomy is further evidence against the latter interpretation. The relatively small gene content of the Y is in keeping with the absence of the congenital defects that characterise other types of sex-chromosome imbalance. This case may therefore be considered as an XYY male.

A more detailed study of the patient's skin and chromosome data for other members of his family will be published later.

A. A. SANDBERG
G. F. KOEPF
T. ISHIHARA
T. S. HAUSCHKA.

The Medical Foundation of Buffalo, and the Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

1. Moorhead, P. S., Nowell, P. C., Mellman, W. J. Battips, D. M., Hungerford, D. A. *Exp. Cell. Res.* 1960, **20**, 613.
2. Sandberg, A. A., Ishihara, T., Miwa, T., Hauschka, T. S. *Cancer Res.* 1961, **21**, 678.
3. *J. Hered.* 1960, **51**, 214.

ALIMENTARY LIPÆMIA AND ISCHÆMIC HEART-DISEASE

SIR,—I should like to comment on the important paper by Dr. Bronte-Stewart.[1]

(1) In those with normal vessels, alimentary hyperlipæmia declines by at least 50% in the four hours after it reaches its peak value. In 60% of patients with atherosclerosis, or with ailments predisposing to atherosclerosis, this decline is considerably slower ("clearing insufficiency").[2]

(2) This phenomenon is difficult to reproduce with fat administered intravenously, because the fat emulsions commercially available ('Lipomul IV', 'Lipofundin', 'Infonutrol', 'Intralipid') have added phosphatide and/or subsidiary synthetic wetting agents ('Pluronic F 68'), which themselves disturb blood-fat transport, and increase the triglycerides and phosphatides. While the phospholipids contained in the emulsions (mainly lecithins) can be metabolised by the body, and their influence on serum fat-content only lasts a short time, synthetic wetting agents (e.g., pluronic F 68) cause a hyperlipæmia which lasts much longer.[3]

(3) By administering a sufficiently large single intravenous dose of fat (150 g. = 1000 ml. of 15% emulsion) it is possible to establish that plasma half-life of the fat introduced is longer in patients with atherosclerotic conditions than in healthy persons.

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Bavaria, German Federal Republic. H. SCHÖN.

PSYCHOLOGICAL TRAINING FOR FUTURE MIDWIVES

SIR,—Some of your correspondents' comments on my Psychological Syllabus for Midwives might have been avoided by closer reading of my syllabus or of your annotation (July 15).

The syllabus contains few of the points which Dr. Le Vay mentions (July 29). I have not said that either long labour or failure to breast-feed stem from rejection of the child by the mother; and the many mechanical factors operating in both processes render such psychological generalisation difficult. The syllabus does not mention sepsis as a factor in puerperal breakdown, though the toxic confusional states have in fact been recognised for years as a complication and some workers have noted a decline in the number of cases they have seen.[4] Two of mine—a mother rehoused after her fourth cæsarean section, and a primipara returning to a one-room flat with her baby after lengthy treatment for pre-eclampsia, a long labour, and forceps delivery—both seemed to me tired and lonely, and their depression lifted with appropriate help. I am sorry if this is Controversial Psychiatry: it seems to me useful experience to pass on to midwives.

I am surprised that Dr. Le Vay thinks that the hysterical patient who is slapped is not made to feel guilty,[5] and that slapping is therefore less serious than blame arising from faulty interpretation by the midwife; but I entirely agree with what her letter implies—namely, that the findings from individual

1. Bouchier, I. A. D., Bronte-Stewart, B. *Lancet*, 1961, i, 363.
2. Schön, H. *Med. Klin.* 1960, **55**, 2195.
3. Schön, H., Flesch, R., Zeller, W., Berg, G. *Med. Welt*, 1961, p. 1473.
4. Seager, C. P. *J. ment. Sci.* 1960, **106**, 214.
5. Tylden, E. *Lancet*, 1952, i, 231.

cases in Freudian analysis form an unsuitable basis for teaching material.

Dr. Dally (July 29) analyses my syllabus as though it was a scientific paper and not notes to guide the reading of lecturers. I am sorry he thinks me presumptuous: I expect I am. But, following the example of many teachers in clinical medicine, I have based my statements on my own work and on the recent literature. So far, apart from the material based on 250 cases which I have already used at various clinical meetings, I have only card-indexed a further 250 of the patients referred to me in two maternity hospitals since 1947. Scraping the bottom of the barrel I also can find 2 cases similar to the one quoted by Dr. Dally, where there was recurrent psychotic breakdown in spite of adequate antenatal and postnatal supportive care. But 15 patients with a history of previous psychotic illness who were given such care did not break down, nor did 2 who were first seen post partum. 4 with a previous history who had not been given psychotherapy broke down again in the puerperium.

I am not surprised that Dr. Dally's cases of postpartum breakdown had adverse personal and family histories; so did mine. Unlike him, I conclude that one should pick out such vulnerable subjects in the antenatal period, and offer prophylactic treatment, instead of attributing a breakdown to "constitutional and genetic factors"—in other words Bad Blood and Fate—and thus condemning the antenatal clinics to therapeutic impotence.

Dr. Mullins (July 22) believes that, when psychology is introduced into teaching, good medical and nursing care fly out of the window. I do not agree with the dichotomy she expresses. I am merely, in my syllabus, stating my own contribution to a concept of the unity of mind and body in the teaching of obstetrics.

University College Hospital,
Obstetric Hospital.
Bromley Hospital,
Psychiatric Department.

ELIZABETH TYLDEN.

FOLIC-ACID DEFICIENCY IN THALASSÆMIA MAJOR

SIR,—In thalassæmia major (Cooley's anæmia) some patients require frequent transfusions; others maintain an intermediate hæmoglobin level for long periods. Among the latter, acute anæmic episodes occur but have been less widely recognised than those in sickle-cell and congenital spherocytic anæmia. The cause and pathogenesis of the acute anæmic episodes, and the recurrent anæmia in thalassæmia major have not been fully explained.

We have found that folic-acid deficiency is an important, heretofore unsuspected, limiting factor in many patients with Cooley's anæmia who require frequent transfusion as well as in those who have acute anæmic episodes. Among 8 such patients so far studied, folic-acid deficiency was demonstrated in 5. In these, administration of folic acid resulted in hæmatological, biochemical, and clinical improvement

In the following case of thalassæmia major, folic-acid deficiency was found; and the need for periodic transfusion was considerably lessened by giving folic acid. For over eighteen months a thirteen-year-old boy required a 250 ml. packed-cell transfusion every four to five weeks to maintain his hæmoglobin level between 6 and 8 g. per 100 ml. Before giving folic acid, the patient's hæmoglobin level was gradually falling from 7·8 g. per 100 ml. The reticulocyte and platelet counts were 3·6% and 228,000 per c.mm. respectively. Marrow morphology was primarily normoblastic, but a few erythroblasts resembled intermediate megaloblasts. The patient's urinary formiminoglutamic acid (FIGLU) concentration before and after histidine metabolic loading was 7·0 and 287 μg. per ml. respectively. Values over 30 μg per ml. after histidine loading indicate folic-acid deficiency.[1,2] Serum-vitamin-B_{12} was 210 μμg. per ml., serum-folic-acid activity 2·7 mμg. per ml.

After giving 20 mg. of folic acid daily by mouth, the hæmoglobin level continued to fall, reaching 6·5 g. per 100 ml. by the fourth day after treatment, but rose to 8·0 g. per 100 ml. by the tenth day. It then remained between 7·1 and 8·0 g. per 100 ml. for over three months. Reticulocytes reached a peak of 16·1%, thrombocytes 1,002,000 per c.mm. Urinary FIGLU excretion reverted to normal after histidine loading. Bone aching and pain occurred for several weeks after folic acid was started, but the patient's clinical well-being improved strikingly. This was the first time in over seven and a half years that this patient's hæmoglobin had been maintained at these levels for so long without blood-transfusions.

Sudden anæmic crises due to folic-acid deficiency occurred in an eleven-and-a-half-year-old patient with thalassæmia major, who no longer required periodic transfusion after a splenectomy twenty months before. Three crises were observed in fifteen months, one after a fracture of the femur, the other two after bronchopneumonia. The hæmoglobin concentration fell from 8·6 to 6·3 g. per 100 ml. in a few days in the first crisis, from 8·2 to 5·6 g. in the second, and from 9·5 to 5·0 g. in the third. Relative reticulocytopenia preceded the decline in hæmoglobin. Marrow morphology was normoblastic during the first crisis, normoblastic but with occasional megaloblasts during the third. Urinary FIGLU concentrations before and after histidine metabolic loading at the time of the first and third anæmic crises were 1·2 and 261 μg per ml.; and 2·4 and 187 μg per ml. respectively. Serum-vitamin-B_{12} levels were 260, 330, and 360 μμg per ml. in the three anæmic crises. Serum-folic-acid activity at the time of the last episode was 4·9 mμg per ml.

After folic acid was given by mouth, in doses of 20 to 60 mg. daily, there was an increase in the hæmoglobin concentration from 6·3 to 8·9 g. per 100 ml., from 5·6 to 9·0 g., and from 5·0 to 10·1 g. respectively after each anæmic episode. Reticulocytes reached peaks of 20%, 21·5%, and 19·0%, respectively. Urinary FIGLU excretion after histidine loading became normal each time. In four years since splenectomy, this patient has never needed a transfusion. Anæmic episodes were promptly alleviated by giving folic acid.

A patient with similar acute anæmic crises was recently reported by Jandl and Greenberg.[3] These authors appear to have found no morphological or biochemical manifestations of folic-acid deficiency in their patient; but a hæmatological response followed oral administration of large doses of folic acid. They postulated that supranormal amounts of folic acid may be necessary for optimal erythropoiesis in patients with the increased red-cell turnover of chronic hæmolytic anæmia, since their patient did not respond to small doses of folic acid intramuscularly.

Whether or not these patients have an increased tissue requirement for folic acid is not yet established. We found an unexpected striking decrease, however, in the ability of such patients to absorb folic acid from the gastrointestinal tract. Peak serum-folic-acid activity levels after oral administration of a 40 μg. per kg. test dose in our second patient, were 11·9 and 19·4 mμg. per ml. by *Streptococcus fæcalis* and *Lactobacillus casei* microbiological assay respectively. In normal subjects of the same age, a similar oral dose gave peak serum values of 50–95 mμg. per ml. with *Str. fæcalis* and 70–140 with *L. casei*. Such decreased gastrointestinal absorption may account in part, if not entirely, for the folic-acid deficiency or borderline folic-acid reserves in these patients, and explain the need for and benefit from increased oral intake of folic acid.

In individuals with borderline reserves, relatively mild infections or pregnancy, which may further increase the requirement of folic acid, may induce frank folic-acid deficiency and a precipitous fall in their hæmoglobin level. An acute anæmic crisis occurred in one of our patients with thalassæmia/sickle-

1. Luhby, A. L., Cooperman, J. M., Teller, D. N. *Amer. J. clin. Nutr.* 1959, **7**, 397.
2. Luhby, A. L., Cooperman, J. M., Teller, D. N. *Proc. Soc. exp. Biol., N.Y.* 1959, **101**, 350.
3. Jandl, J. H., Greenberg, M. S. *New Engl. J. Med.* 1959, **260**, 461.

cell double trait in the last three months of two successive pregnancies.

Our findings suggest that folic-acid deficiency is an important and common complicating factor in the acute and chronic anæmia of many patients with thalassæmia major. Reduced gastrointestinal absorption of folic acid is probably one of the causative factors. The folic-acid deficiency was most clearly revealed by increased formiminoglutamicaciduria after histidine metabolic loading. It is of diagnostic and theoretical interest that moderate to severe folic-acid deficiency existed in the absence of megaloblastic characteristics in the erythroid or myeloid series of the blood and marrow. Folic-acid deficiency would not have been suspected on morphological grounds in most of our patients. The hæmoglobin level was increased or maintained, and the biochemical and, when present, the morphological manifestations of folic-acid deficiency disappeared after giving folic acid.

These observations raise expectations of a new therapeutic approach to the acute and recurrent anæmia in this chronic disease and of a means to reduce the need for transfusions.

These studies were supported in part by a grant-in-aid from the Cooley's Anæmia Blood and Research Foundation for Children (New York) and the U.S. Public Health Service.

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A. LEONARD LUHBY
JACK M. COOPERMAN.

PREMEDICATION WITH ATROPINE BY MOUTH

SIR,—I read with interest Dr. Dimsdale's comments (May 20) on the excellent article by Dr. Joseph and Dr. Vale on oral atropine.[1] I would like to endorse most heartily the more widespread giving of drugs orally and the attempt to limit the innumerable and quite often needless injections carried on in hospitals.

On the other hand, I am a firm believer in intravenous induction in the anæsthetic room or dental surgery performed by a competent anæsthetist using new small needles. This procedure can be nearly painless.

As far as oral atropine is concerned, I have now changed from 0·8 mg. (gr. $^1/_{75}$) to 1·2 mg. (gr. $^1/_{50}$) and find a big improvement. Nevertheless there are conditions in which atropine should be injected. If an irritant anæsthetic—e.g., ether—is given, then in my experience gr. $^1/_{50}$ atropine by mouth is not as effective as gr. $^1/_{100}$ by injection.

Asquith and I[2] when investigating the longer-acting 'Hyperduric Atropine', similarly found it quite satisfactory provided ether was not administered. Ether will probably be given more rarely now that halothane has been introduced and with the advances in pædiatric anæsthesia with nitrous oxide and oxygen and controlled respiration with muscle relaxants.

Finally, why not give sedatives postoperatively by mouth instead of by injection. Most patients, excluding those who have had abdominal operations, can take this sedation by mouth; and provided it is given in larger doses than by injection it is highly effective.

How ridiculous it is to see a fit young man having a cup of tea and a slice of toast postoperatively after, say, a meniscectomy, and a nurse injecting 100 mg. pethidine or gr. $^1/_4$ morphine subcutaneously.

Little Bromwich General Hospital,
Birmingham, 9.

EUGENE THOMAS.

A MODIFIED ARTERIAL FILTER ASSEMBLY FOR THE MELROSE HEART-LUNG MACHINE

SIR,—When perfusing dogs with this machine, one apparently inexplicable death drew attention to the possibility of small air-bubbles passing through or round the filter screen.

Experimental runs were then carried out in the laboratory with dextran—a fluid similar to blood, but clear so that any air bubbles could be photographed. Photographs were taken with a high-speed electronic flash of 1/1000th sec. duration to freeze movement.

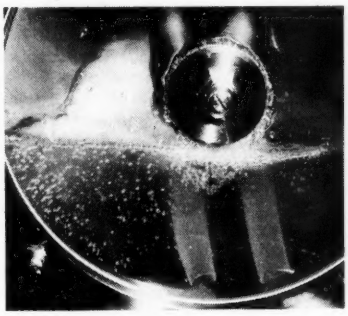


Fig. 1.

While the machine was running, small and minute bubbles could be demonstrated with pump and oxygenator turning at 36 r.p.m. (2 litres per min.). Bubble formation was much increased by increasing the flow-rate, or by allowing the level in the oxygenator reservoir housing to fall below the central fulcrum pin. Fig. 1 shows this very clearly; the pump and oxygenator were running at 67 r.p.m. (3·7 litres per min.).

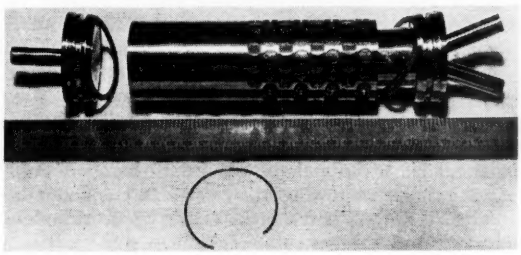


Fig. 2.

Further photographs proved that, unless the stainless steel wire mesh inside the filter was precisely assembled as detailed below, small air bubbles, though invisible to the naked eye, could pass into the arterial line. The greater the rate of perfusion, the more air-bubbles could be photographed which had escaped filtering. A similar picture resulted if the reservoir level in the oxygenator was allowed to fall well below the central fulcrum pin (seen in fig. 1), even at low perfusion-rates.

Being potentially lethal, this intermittent filter failure was remedied, before any patients were perfused, by the following modifications:

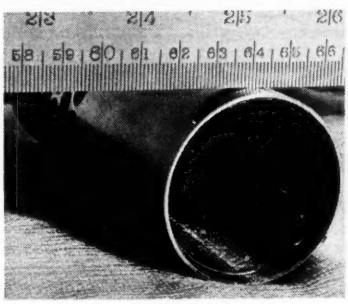


Fig. 3.

(1) Special soft silicone rubber seals in which the stainless steel wire mesh ends would embed under compression were made. (44·5 mm. internal diameter × 51 mm. external diameter × 2 mm. thick, silicone rubber E.360.)

(2) The wire mesh, cleaned in ether to remove grease and metal dust, is examined for weaving flaws, and then fitted inside the supporting cylinder exactly endwise. The inside overlap is $^3/_4$ in. (fig. 2).

(3) Close overlap and constant positioning during assembly of the complete filter is guaranteed by three expanding stainless steel circlips fitted in the middle and near each end (fig. 3).

After these modifications, repeat tests and photographs showed that no air-bubbles passed the filter whatever the rate of perfusion. Obviously air *can* pass the filter if its air-trapping

1. Joseph, M. C., Vale, R. J. *Lancet*, 1960, ii, 1060.
2. Asquith, E., Thomas, E. *ibid.* 1948, ii, 930.

capacity is exceeded—but these modifications completely check inefficient filtering.

The formation of bubbles in blood during actual perfusion is very similar to that shown in fig. 1, but is naturally not at all easily seen. Whatever the combination of plates in the oxygenator, and depending on the rate of perfusion, more or less bubbles are bound to be generated, hence the importance of the pump operator being absolutely sure that his filter is 100% efficient. Some workers have suggested "silicone emboli" as an explanation of undiagnosed postperfusion symptoms—I would suggest small diffuse air emboli as being the more likely cause.

During our third perfusion the modified filter had an unexpected test. Accidental surgical occlusion of the venous return reduced the blood level in the oxygenator reservoir to just above the pump pick-up tubes seen in fig. 1. Rapid correction of this still left a filter containing a large quantity of air-bubbles, which was immediately blown out of the top tube. The patient had no signs of emboli at any time.

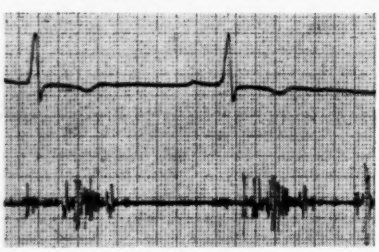
My grateful thanks are due to Sister S. F. Deguillame and Mr. R. Gregory for their assistance.

The special silicone rubber seals are made by James Walker & Co., Lion Works, Woking, Surrey.

The London Chest Hospital, E.2. R. N. G. ATHERSTONE.

ABDOMINAL BRUIT IN RENAL HYPERTENSION

SIR,—The progress of reparative surgery in cases of renal-artery hypertension (Goldblatt type) has given a new impetus to the search for diagnostic procedures. Aortography,[1] the Howard-Rapoport test,[2 3] the Etamon test,[4] and radioisotope renograms [5] are the most widely recommended investigations. An often forgotten simple bedside test for narrowing of a renal artery is abdominal auscultation [6–9] A harsh bruit in the upper abdominal quadrants and paravertebral region can often be heard with the bell of the stethoscope if constant but energetic pressure is exerted (see figure). A grade 3/6 systolic bruit



Systolic bruit in a patient with unilateral narrowing of a renal artery.

at the right side of the abdomen or lower back is very suggestive of narrowing of the right renal artery because heart murmurs are seldom transmitted to this side.

In 10 of 14 patients with sustained hypertension related to narrowing of one or both renal arteries (13 cases) or to renal infarction (1 case), a systolic bruit was heard.[10] This acoustic sign would not be expected in the patient with renal infarction (see below).

Vascular tones are not to be confused with a bruit and are normally heard in arteriosclerotic patients. Systolic or continuous murmurs can be heard in the upper abdomen in patients with coarctation of the abdominal aorta, arteriovenous shunts, aneurysm of the abdominal aorta or side arteries, coronary arteriovenous shunts, or large hæmangiomas, and in pregnant patients. A short bruit can be related to kinking and lengthening of the iliac arteries in arteriosclerotics.

The 14 patients we observed with renal hypertension can be classified as follows:

Condition	*No. of patients*	*No. with a bruit*
Unilateral narrowing of a renal artery (4 right, 2 left)	6	4
Bilateral narrowing of the renal arteries	2	2
Unilateral narrowing of renal artery, other side hypoplastic	2	2
Unilateral narrowing of renal artery and hypoplastic kidney	1	0
Congenital hypoplastic abdominal aorta and hypoplastic renal arteries	1	1
Complete occlusion of the abdominal aorta at the level of the renal arteries	1	1
Renal infarction	1	0

These findings suggest that narrowing of a renal artery not infrequently causes hypertension, particularly in young individuals. Patient and careful anterior and posterior auscultation over the kidney regions is a valuable and simple aid to diagnose many of these cases and select more efficiently the patients for aortography and other cumbersome investigations.

M. VERSTRAETE
P. LAUWERS
H. KESTELOOT
J. V. JOOSSENS.

Department of Medicine, University of Louvain, Belgium.

EFFECT OF *d*-THYROXINE ON SERUM LACTESCENCE

SIR,—After fat ingestion, visible lipæmia normally reaches a maximum in about four hours. The increase in turbidity is largely due to rises in serum-glycerides. Patients with coronary-artery disease often show persistent serum lactescence, which is more intense and lasts longer after meals.[1 2] Alimentary hyperlipæmia may precipitate attacks of angina pectoris in these patients by reducing oxygen diffusion to the myocardium.[3 4] In addition, hyperlipæmia reportedly shortens blood-clotting time.[5] Treatment of atherosclerosis, therefore, may best be directed towards improving fat tolerance as well as reducing specific serum-lipid fractions.[6]

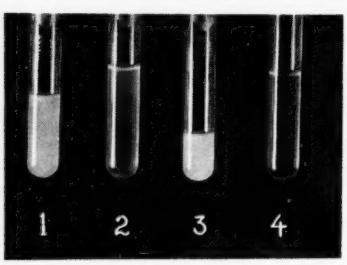


Fig. 1—Sera from 2 patients with coronary-artery disease showing lactescence before sodium *d*-thyroxine therapy (tubes 1 and 3) and after five months of it (tubes 2 and 4).

We recently evaluated the clinical effectiveness of sodium *d*-thyroxine in the management of atherosclerotic hyperlipæmia in 22 patients with severe coronary-artery disease. After initial blood-sampling, the patients were given 2-4 mg. of sodium *d*-thyroxine daily, progressively increased over a four to five month period to a maximum of 6 or 8 mg. per day. During treatment blood-samples were taken twice a week.

Sera from 10 patients in the study group were visibly lipæmic before sodium *d*-thyroxine was given. In specimens collected after treatment lactescence was greatly reduced (see fig. 1).

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3. Kuo, P. T., Joyner, C. R., Jr. *J. Amer. med. Ass.* 1955, **158**, 1008.
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5. Poole, J. C. F. *Brit. med. Bull.* 1958, **14**, 253.
6. Kuo, P. T. *Med. Clin. N. Amer.* 1960, **44**, 1635.

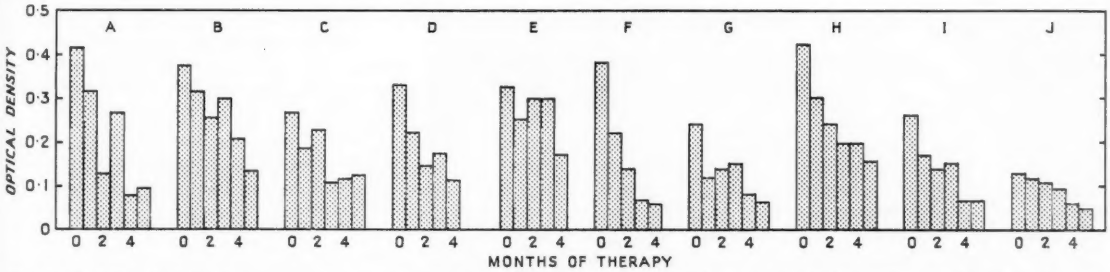

Fig. 2—Serial optical-density measurements on sera obtained before and at monthly intervals during sodium *d*-thyroxine therapy.

Aliquots of sera obtained from the 10 patients at monthly intervals were diluted with saline (1/10). Optical density measurements were then made in a 'Coleman Universal' spectrophotometer at 440 mμ. Pretreatment sera from these individual had optical densities ranging from 0·130 to 0·420 (mean 0·338), whereas after four to five months of therapy values ranged from 0·050 to 0·175 (mean 0·113) (see fig. 2). Thus an average reduction in optical density of more than 60% was evident during the study period. Most patients exhibited a trend toward step-wise declines in serum-lactescence, while the greatest decreases were noted in those with the highest initial values. Sera from patients F, G, I, and J no longer appeared lipæmic on inspection after four to five months of sodium *d*-thyroxine therapy. It is noteworthy that in patient J optical density was demonstrably depressed despite only a mild lipæmia before treatment.

Sodium *d*-thyroxine was well tolerated by the patients during the period of the study. Doses of 6 to 8 mg. of the drug did not aggravate or induce angina pectoris. By contrast, 3 patients reported that the frequency and severity of their angina and dyspnœa had decreased. It is tempting to speculate that reduction in lipæmia might be partially responsible for the alleviation in these symptoms. The level of lipæmia appears to influence oxygen uptake in the lungs as well as oxygen release to the myocardium.[3]

This investigation was supported in part by grants from the American Osteopathic Association the United States Public Health Service, Baxter Laboratories, and the Attending Staff Association of the Los Angeles County Osteopathic Hospital.

Los Angeles County Osteopathic Hospital, College of Osteopathic Physicians and Surgeons, Los Angeles, and the Cardiovascular Research Center, Burbank, California, U.S.A.

R. L. SEARCY
J. S CARLUCCI
V P. CARROLL, Jr.
G. S. GOUGH
L. M. BERGQUIST.

RUPTURE OF A CARDIAC CATHETER

SIR,—Since Ross and his coworkers [1] published their method for transseptal left atrial puncture, there has been an increasing interest in this technique.[2–4] Our experience has been that it is a safe procedure, giving valuable information. Location of the needle electrode can be enhanced by recording intra-auricular electrocardiograms of the top of the needle point. But recently we encountered a complication which to the best of our knowledge has not been described before.

The ruptured catheter.

A right-heart catheterisation was performed in a man of forty through an exposed right saphenous vein. A flexible Ross needle was introduced through a no. 9 Lehmann catheter with its tip in the right atrium. The catheter bent slightly, presumably at the junction of the external iliac vein with the right common iliac vein. At this point resistance was felt to the introduction of the Ross needle, which was overcome by applying slight pressure and rotating the needle. The patient experienced a sharp pain, radiating to the leg. The needle and the catheter were immediately withdrawn. It turned out that the catheter was perforated at the point where bending had been noted previously (see figure). There were no subsequent complications. Before introduction, the catheter had been carefully inspected, and no defects had been detected.

We conclude that if the course of the catheter is not straight this procedure should be carried out only with the utmost care. The needle should always be passed through the catheter under fluoroscopic control.

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4. Ross, J., Jr., Braunwald, E., Morrow, A. G. *Circulation*, 1960, **22**, 927.

University of Amsterdam
Department of Cardiology,
Wilhelmina-Gasthuis,
Amsterdam, the Netherlands.

J. E. JAPIKSE
F. L. MEIJLER.

PROTECTION FOR A HÆMOPHILIAC

SIR,—A hæmophiliac of 23 months was recently admitted to the pædiatric department of this hospital, with bleeding into the tissues around his elbow-joints.

In the past, he had been admitted on several occasions with bleeding from the gum margins after falling on to his chin and knocking into objects such as furniture.

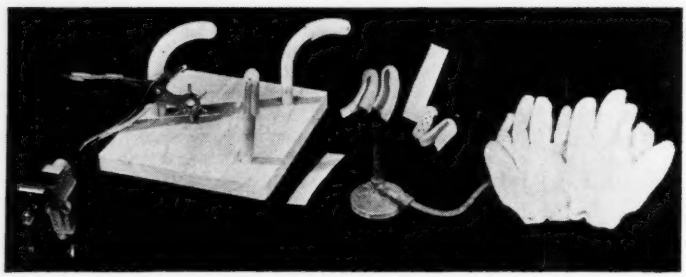
We advised strapping foam-rubber pads around the vulnerable joints; and, to limit injuries to the face and head, we have had a boxer's head guard with a chin-protector modified to fit him. Since his discharge, he has been wearing this at home quite happily; I enclose a recent photograph. I gather from the mother that his falls are much less troublesome, and he has been able to roam about his home without having to be so closely observed and restricted.

Chester City Hospital,
Chester.

JOHN H. LLOYD.

POLYETHYLENE SPLINTS FOR CASUALTY WORK

SIR,—Few of us can have worked long in industrial or hospital casualty departments without becoming aware of the shortcomings of plaster-of-paris for protecting fingers and toes. It is messy to apply, takes time to set,



and is quite heavy. It soon gets wet, dirty, or loose, and then has to be renewed.

Much time can be saved at peak periods by an assortment of polyethylene splints prepared at slack times by doctors or nurses. Besides being light, these splints are hygienic, and after conventional sterilisation can be used again and again. Their initial cost is about the same or a little less than that of plaster-of-paris.

For a start, short, straight, protective caps can be moulded very easily around formers made from $^1/_2$ in., $^3/_4$ in., 1 in., and $1^1/_4$ in. diameter wooden dowel rods, with their ends smoothed by sandpapering. Strips about 1 in. wide and 4 in. to 5 in. long are cut from $^1/_{16}$ in. sheet polyethylene. The strips are warmed carefully over a bunsen burner; an old pair of gloves should be worn to protect the hands. The polyethylene becomes pliable as soon as it becomes transparent; but if it is taken beyond this stage, it will melt or burn. When transparent, the strip is held in place around the former and allowed to cool. It can then be eased off and is ready for use. The dowel rods can be conveniently held in position in sockets in a base-board or fixed in a small vice (see figure).

The splints are very adaptable and can be used for many different injuries and digit-sizes if their sides are left open. They can be incorporated most readily under a superficial layer of ' Tubegauze ', or held in place by a turn of ' Elastoplast '. If extra ventilation is required they can be readily pierced with a leather punch or trimmed with scissors.

To cover a finger more completely curved splints can be used; suitable formers can be made by a woodworker from ash dowel rod, bent as required by treatment with steam.

These splints are very popular with patients and staff for treating crushed toes and fingers, whether fractured or not. There are some reports of their use elsewhere.[1–5] A British Standard on polyethylene splints has recently been issued.[6]

$^1/_{16}$ in. thick polyethylene is obtainable in sheets, 3 ft. × 3 ft., from Stanley Smith & Co., Worpoe Road, Isleworth, Middlesex. A sheet costs about 36*s*. The cost of a splint works out at 1*d*. or 2*d*.

I should like to thank the sister-in-charge and the physiotherapists for their interest and help in designing the splint.

Morris Motors, Ltd., Cowley, Oxford. W. G. WHITE Senior Medical Officer.

INHIBITORY EFFECT OF COLCHICINE ON TRANSPLANTABLE SKIN FIBROMAS

SIR,—Recently I described a multiple fibroma of the skin in the common newt *Triturus vulgaris*. This was characterised by a distinct enlargement of the adepidermal reticular network [7–10] and appeared to be transplantable in the same animal.[9 10] As colchicine inhibited this tumour,[11] it seemed desirable to perform a corresponding investigation on another lower vertebrate fibroma to establish whether the results obtained had more general significance.

For this purpose, skin fibromas in the axolotl, *Ambystoma tigrinum*, were studied. The material was obtained by breeding the normal animals of the first litter in which the tumour was found. Fragments of tumour tissue from the vicinity of small tumours, in which an enlargement of the nodular swellings of the adepidermal reticular network might be expected, were transplanted to a perfectly tumour-free region of the same axolotl, preferably in the tail-base area. In 11 of the 13 cases a distinct tumour developed after about four weeks at the site of transplantation, whereas in the 2 negative cases the transplanted material was almost completely resorbed. After four weeks, in 8 of the 11 animals with tumours colchicine treatment was started, the remaining 3 axolotls being used as controls. This treatment consisted in giving an intraperitoneal injection once a week of colchicine-saline solution (0·0017 mg. colchicine). The method of preparing the solution for injection was the usual one.[12–14] The experiment lasted ninety-five days.

By comparing the area diagrams of the tumours, it was clear that colchicine had an inhibitory effect on the growth of this fibroma. The tumours in the colchicine-treated axolotls as well as those in the control animals were examined microscopically, and the adepidermal reticular network in particular was studied with the aid of Pap's ammoniacal silver method as modified by Mitchell and Wislocki [15] (and counterstained with paracarmine), and Bodian silver-proteinate (counterstained with orange G). The tumours of the control animals exhibited the normal course of development of this fibroma, and the following stages already described in the newt [9–11] were found: (a) enlargement of the nodular swellings of the adepidermal reticular network; (b) continued enlargement of the nodular swellings and concentration of fibroblasts in their vicinity; (c) formation of new fine fibrils radiating from the enlarged nodular swellings, a densely structured network thus being formed around the concentrated fibroblasts; (d) fusion of the concentrated masses of fibroblasts to larger complexes. The enlarged nodular swellings are probably induction centres which, with the acid of certain chemical substances, cause the local concentration of the fibroblasts. In the tumours of the colchicine-treated axolotls the enlargements of the nodular swellings and the concentration of the fibroblasts in particular appeared to be disturbed. Therefore the effect of the colchicine is in all probability an inhibition of these processes. The fact that in the colchicine-treated axolotls these processes, as well as the tumour growth, had been halted is sound evidence for the assumption that these processes of the adepidermal reticular network play an important part in the development of this skin fibroma. These results agree well with the data obtained in the newt,[9–11] and consequently have a certain general significance.

Histological Laboratory, Free University, Amsterdam. A. STOLK.

"INCURABLY OF UNSOUND MIND"

SIR,—A petition for divorce on grounds of incurable unsoundness of mind was dismissed by Mr. Commissioner Latey, Q.C.[16]

After seeing the respondent husband in the witness-box for an hour or so the judge accepted him as "a reasonable man and a truthful witness and a person fully qualified to manage his own affairs". "He was clear, thoughtful, and logical in his answers and gave every appearance of being a sounder witness than many parties in matrimonial causes." The

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16. See *Lancet*, Aug. 12, 1961, p. 366.

judge " could not find that he was incurably of unsound mind, or even that he was of unsound mind".

Experienced judges can form very accurate impressions of veracity, guilt, integrity, and character from a person's appearance and behaviour in the witness-box; but I dispute their competence to adjudicate on unsoundness of mind on the same basis.

Paranoiacs are often highly intelligent and extremely plausible. It may be very difficult indeed to find any flaws or discrepancies in their statements. They are capable of concealing their delusional themes for long periods; and it may require relatively protracted observation by skilled and experienced mental specialists to establish a diagnosis.

If indeed this was not fully appreciated by the powers that be it would surely be unnecessary for patients suspected of mental disorder to be detained in hospital for a minimal period of 72 hours to enable a decision to be reached on the need for treatment, &c.

It would appear that the old adage about shoemakers keeping to their lasts is no longer applicable in respect of judges on matters of mental illness.

London, W.1. ELLIS STUNGO.

R.C.S. ANNUAL MEETING IN SHEFFIELD

SIR,—I am grateful to you for allowing me to use this opportunity of bringing to the notice of the profession that the College is holding its annual meeting this year on Nov. 24 and 25 in Sheffield.

As you know, the College has recently adopted the policy of holding meetings from time to time in provincial centres, and the last of these was held in Cardiff in 1958. The purpose of the council in holding these meetings is to bring the College closer to its provincial Fellows and Members and to enable them to take part in some of its activities. The council is particularly anxious that Members of the College shall join us at this meeting, and any other diplomates will of course be very welcome. Fellows will be notified individually.

The meeting will commence with a subscription dinner on Friday Nov. 24 in the Cutlers' Hall. Tickets for the dinner (£2 12*s*. 6*d*. each) can be obtained from the secretary of the College, but numbers are limited, and early application is necessary. Fellows and Members may apply to bring male medical or non-medical friends as personal guests.

On Saturday, Nov. 25, the morning will be devoted to scientific exhibitions and films at the new teaching hospital, followed by a fork lunch, kindly given by the board of governors of the United Sheffield Hospitals in the refectory of the university.

In the afternoon the statutory annual meeting of Fellows and Members will be held in the Firth Hall, and this will be followed by the conferment of the honorary fellowship of the College on Sir Howard Florey, P.R.S., who will afterwards deliver the Arthur Hall lecture (under the auspices of the Arthur Hall trustees).

The council hopes that this meeting will prove to be as successful an event as was the meeting in Cardiff, and we trust that our colleagues in Yorkshire and the Midlands will make a special effort to attend.

Royal College of Surgeons of England,
Lincoln's Inn Fields,
London, W.C.2. ARTHUR PORRITT.

GREEN FOR DANGER

Dr. M. F. Cuthbert, medical adviser to Pharmax, Ltd., writes:

In your leading article (Aug. 12) you refer to ' Colistin ' (colymycin) as " a mysterious Japanese antibiotic ". Extensive clinical trials are at present in progress in this country and preparations are being made to market this antibiotic.

Colimycin was isolated in 1950 by Yasou Koyama [1] from a microorganism from the soil, *Bacillus colistinus*. Structurally [2] it is a cyclic polypeptide containing *l*-threonine, *d*-leucine, *l*-leucine, and $\alpha\ \gamma$ diaminobutyric acid. The free amino group of diaminobutyric acid is conjugated with 6-methyl-octanoic acid to form a side-chain. In Germany this antibiotic is called ' Colistin,' and in the United States ' Coly-mycin '.

The antibacterial spectrum has been established by Courtieu,[3] who found colimycin to be effective in its bacteriostatic and bactericidal action against gram-negative organisms, including strains often found resistant to other antibiotics. The spectrum includes the Escherichia, Klebsiella, and Pseudomonas groups. It appears, however, that colimycin is ineffective against the Proteus group.

Clinical experience in France and Italy,[4–8] and more recently in the United States,[9 10] has shown colimycin to be of definite value in the treatment of urinary, systemic, and gastrointestinal infections due to gram-negative organisms, especially resistant strains, and has confirmed the non-toxicity of the antibiotic. Infections due to *Ps. pyocyanea* represent a major indication for colimycin.

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11. Annual report (1958) of Dr. R. W. Elliott, M.O.H. for the West Riding.

Public Health

Sweets and Snacks and Dental Caries

EVERY year, well over a million permanent teeth of school-children are filled, and something like half a million extracted, by the School Health Service. And the incidence of dental caries is in fact even higher than these figures suggest. Of children aged five, about 8% are said to be free from dental caries, but of those between eight and twelve, only 3%. The proportion leaving school with perfect dentition is certainly less than 1 in 50; and we may fairly say that the disease now attacks almost every child.[11] At a time when the health of children is in many ways so much better, it is particularly galling that their dental condition is worse than it was in the period of sweet-rationing immediately after the war.

On the advice of their school medical officers, some education authorities have taken a new step by declaring war on the sale of sugary and starchy foods in the school tuckshop. Biscuits and sweets have been prohibited, despite occasional pleas from head teachers who were troubled about the loss to school welfare funds, maintained by the profits of the shop. To abate the pangs of hunger felt nowadays between meals by so many young children, potato crisps, nuts, raisin, and icecream are all that are allowed in some schools. Apples and bananas are recommended, but one must recognise the validity of the objections to them—the difficulties of purchase (and the high cost of fruit even in the " glut " year of 1960), of storage and wastage of bulky fruit, and, not least, of the safe and satisfactory disposal of the apple core and banana skin.

A further difficulty arising over the sale of nuts to the younger children is that the nut may " go down the wrong way " and cause suffocation. Not long ago, two children of primary-school age, cyanosed from suffocation, were rescued in the nick of time. A recent coroner's inquest on the death of a Salford child of five recorded that a child had suffocated, while chewing nuts, after being slapped on the back by a playmate. The sale of

nuts might well be restricted to children of secondary-school age.

It is depressing to study the reports of school dental officers and to note in particular the great frequency of the adjective " appalling " in their description of the present epidemic of dental caries. For the disease—painful, harmful, and wasteful—is almost entirely preventable.[2]

In industrial areas especially, the condition of children's teeth appears to be still worsening with the greater sale of lollies (iced or otherwise), in addition to the sweets, cakes, buns, chocolate, biscuits—and worst of all, the toffee. The regular consumption of such things between meals is hardly ever necessary for children if the meals themselves are suitable; and perpetual consumption of sweets is no more than a bad habit, arising from custom, which neither wise parents nor wise authorities would encourage.

Since, unhappily, the habit is very widely ingrained in this country, the question arises whether the food industry might not be somehow induced to provide food which would not favour caries or obesity and which could be readily distributed with the mid-morning school milk. When we see the ingenious processing and refinements of which the industry are capable, we wish that they would devote some of their researches to a wholesome and convenient substitute for the cariogenic and calorific snack.

2. *Lancet*, 1960, i, 156.

Obituary

HENRY HOWARTH BASHFORD

Kt, M.D. Lond., F.R.C.P.

Sir Henry Bashford, a former medical adviser to the Treasury and a former chief medical officer of the Post Office, died on Aug. 15 at the age of 81. At the Post Office he had access to a unique collection of medical records, and his enlivening contribution to industrial medicine was largely based on his gift for extracting clinical wisdom from statistical abundance.

He came of a family with varied interests and talents. One of his grandfathers was a naval captain, who as Lieutenant Bashford was wounded on board the *Royal Sovereign* at Trafalgar; the other, the Rev. Henry Howarth, was chaplain in ordinary to Queen Victoria. Bashford himself was educated at Bedford Modern School and spent some years in Canada before deciding to study medicine. He qualified from the London Hospital in 1904 and three years later entered the Post Office medical service.

Walter Stoneman

He found there, as he once said, unworked mines of information both for industry and medicine. Records had been kept since 1855, and under Bashford's supervision there were soon available comprehensive sickness records of nearly a quarter of a million men and women aged 16 to 60. But he was not content to be a passive spectator of these accumulations, and he was soon using them to destroy medical bogies. The gravity of adolescent albuminuria, loss of wages as an incentive to return to work, and quarantine for healthy contacts were some of the subjects which he showed could be usefully reappraised. He also published papers on tuberculosis and peptic ulcer, and comparative statistics on the physique of young workers.

In 1933 Bashford was promoted to be chief medical officer of the Post Office, an appointment which he gave up ten years later to take over the newly created post of Treasury medical adviser. Here he acted as consultant on problems of welfare, environment, and health for the Civil Service as a whole and especially for Departments which had no medical adviser of their own. He retired in 1945.

In 1938 he was created a knight and the following year he was elected F.R.C.P. He was an honorary physician to the King from 1941 to 1944. He was also for some years a member of the Industrial Health Research Board.

Bashford's skill and delight in writing were clear even in his professional papers, and he was the author of several novels, a book of poems, stories for children, and hints for fellow fishermen. He always stressed the importance of humanising medicine, and a series of letters from *The Corner of Harley Street* (which were first published under the pseudonym of Dr. Peter Harding) ranged wittily but wisely over such subjects as an old aunt's leaning to quackery, the teaching of sex to children, and modern journalism. He edited a book of selections from a *Lancet* series which appeared under the title of *Doctors in Shirtsleeves*. The pleasures and interests of his years of retirement at Pewsey were recaptured in *Wiltshire Harvest*.

J. T. writes:

" The fundamental structure of Harry Bashford's personality was an abounding and humble-minded humanity. He asked for little and he gave much to his fellow men. In lighter vein he had a remarkable facility for apt and trenchant topical rhyming. When he was a resident in the house at the London Hospital there would appear almost daily on the receiving-room officers' notice-board some such couplet as this:

> What higher lot can fall to man's ambition,
> Than giving oil and malt for malnutrition,
> Or regulating juvenile excreta
> With pellets of hydrargyrum cum creta.

He loved his garden; he loved his fishing and all Nature; he loved his pictures. He spoke no ill of any man and none spoke ill of him."

V. C. M. writes:

" Many people may extol the late Sir Henry Bashford's professional merits, or his ability as a writer, but fewer knew him as the warm-hearted, tolerant, broadminded, and helpful man he was. He was interested in scholarly pursuits, but he was also keen on nature studies, country walks, fishing and canoeing, and, from his youth, he knew all about the farmer's life. He loved good food, good wine, and fine old silver, and he was an expert on painting, himself being no mean draughtsman. It was interesting to see his enthusiasm even in abstract painting and many a young artist was encouraged by a generous fee paid from modest private funds.

"He and Lady Bashford always kept an open house of such warmth and gaiety that it delighted their friends, and after her death six years ago he carried on the tradition. He had travelled widely and met interesting people and it was not surprising that he was a raconteur of the first order. There was humour in his stories, knowledge of mankind, humility, and wisdom, but never malice. Above all he loved people. Those who know of the hard struggles of his youth will be able to tell how he mixed, lived, and worked with the rich and the poor, the humble and the proud, the intellectuals and simpletons; and, when he could, he gladly helped them all."

Lady Bashford was Margaret Eveline Sutton. They leave three daughters and a son who is the headmaster of Wellingborough School.

HENRY THOMPSON BARRON

M.D. Lond., M.R.C.P.

Dr. H. T. Barron, who died on Aug. 12 at the age of 85, was consulting physician in diseases of the skin at Westminster Hospital, London.

He went to Westminster Medical School as an entrance scholar in 1893 and qualified in 1898. After house-appointments he graduated M.D. in 1900 and was appointed medical registrar at Westminster Hospital with a view to becoming a consultant physician. Shortly after this, however, his father, a Congregationalist minister, died unexpectedly, leaving a widow and some younger brothers and sisters. In order to help his mother, Dr. Barron threw up his hospital appointment and went into general practice in Streatham, where he rapidly became one of the most popular practitioners. Not wishing to lose touch with his old hospital he made a point of attending whenever he could the famous Wednesday afternoon skin clinic of the late Dr. Colcott Fox. Here he rubbed shoulders with most of the men who were later to be the leaders in dermatology in London, for at that time the training of a London dermatologist was incomplete without his having sat for a time at Fox's feet. Later when Dr. S. E. Dore succeeded Colcott Fox, Barron became a clinical assistant in this department.

In 1927 he took the M.R.C.P., and shortly afterwards he was appointed assistant physician to the skin department of Westminster Hospital. On the retirement of Dr. Dore in 1933, he was appointed physician to the skin department; and, although due to retire in 1940, he stayed on until 1945 to help with the work during the war.

J. L. F. writes:

"Dr. Barron was a shrewd and kindly physician, and his years of general practice stood him in great stead when he later became a specialist. He was an expert in the handling of patients, a good diagnostician but a little bit impatient with the fussy over-classification that was coming into vogue in his specialty towards the end of his time. He was also a sound teacher.

"Dr. Barron was an early motorist and claimed to be the first medical man in South London to use a motor-car for professional purposes. In his later years he delighted in telling stories of hair-raising adventures on the London-Brighton road, where everything possible seemed to have gone wrong and yet eventually the journey was completed successfully. In the 1930s his diminutive figure, perched in the driving-seat of an enormous yellow Buick, was one of the sights of the old Westminster Hospital.

"From his school days he was a fine conjurer and he became a member of the Inner Magic Circle. One of the highlights of his year was the annual dinner of the Magic Circle, where he would entertain twenty or more guests. A good judge of food and wine, he was fond of dining out, and between the wars could be found most Saturday nights at his usual corner table in his favourite Soho restaurant where he and his wife liked to entertain their friends."

Dr. Barron's wife predeceased him. There were no children of the marriage.

WALTER FERGUSSON LEISRINCK HANNAY

Kt, M.R.C.S.

Sir Walter Fergusson Hannay, who died on Aug. 14 at the age of 56, had served in many London hospitals, and in his practice in Harley Street he maintained his special interest in dermatology. He was also concerned with present-day health hazards, such as noise and diesel fumes, and he was associated with the work of the Noise Abatement Society and the National Pure Water Association.

He was educated at Berkhamsted School and qualified from Guy's Hospital in 1928. After a resident appointment at Guy's he held a series of clinical assistantships at London hospitals, including Princess Beatrice Hospital, the National Heart Hospital, the West End Hospital for Nervous Diseases, and St. Mary's Hospital. Though his practice grew steadily he found time to act as a medical consultant to the Saturday Hospital Fund and the Open Way Clinic and he was knight chirurgeon to the Knights of the Round Table. He was a member of many London medical societies including the Royal Society of Medicine, the Medical Society of London, the Harveian Society, the Osler Club, and the Chelsea Clinical Society, of which he was a past president. Lord Attlee was for many years one of his patients and he was knighted in the resignation honours in 1951.

R. C. writes:

"Fergusson Hannay will be missed by many, and not least by those who were at Guy's in the middle '20s and knew him well. Of fresh complexion and with a mass of reddish hair, he was a personable figure and remained so all his life. The academic life had no great attraction for him and he quickly settled in general practice in Chelsea and later found a wider field for his talents in the West End. He belonged in many ways to the older generation of doctors, with an oldfashioned courtesy to strangers and an unaffected geniality to his contemporaries. He held the office of president of the Chelsea Clinical Society with grace and distinction. Success and honours came to him relatively early in life and he had the spiritual grace to let neither spoil him, and perhaps no man could have a more fitting epitaph than this."

Sir Walter is survived by his widow Doris Leslie, the historian and novelist.

SONNY SNEIR DAVIDSON

M.R.C.S.

Dr. Sonny Davidson, physician to the London Clinic for Psychoanalysis, died at the age of 50 on Aug. 7 as the result of an accident while on a fishing holiday.

After qualifying from Guy's Hospital in 1938, he spent several years in general practice. During the late war he served in the R.A.M.C. and afterwards he trained as a psychoanalyst. He was on the staff of the Cassel Hospital from 1948 to 1954, and since then had been in private psychoanalytical practice.

A colleague writes:

"Dr. Davidson's chief characteristics were his intense interest in anything and everything to do with people, and his generosity. He met the vicissitudes of life, his own and other people's, with an unselfconscious acceptance of reality, and his natural and sincere approach made possible a refreshing freedom in discussion and conversation. His attitude was serious and unsentimental, and he never denied difficulties just because he did not know the answer; he would rather say 'Well—there it is'. His concern about the human dilemma, and his conviction that something could be done about it, found expression in his work as a psychoanalyst. He soon became convinced of the importance and validity of Melanie Klein's work, and was an enthusiastic pupil of hers. In addition to being a training analyst he had a special interest in psychotics and in child patients, and he believed that working with little children was fundamentally helpful in the approach to psychotic illness. He read several papers on his work with psychotics to his psychoanalytical colleagues, but for reasons of professional discretion these have not yet been published. He was a man of unflagging energy and worked extremely long hours, but he still found time to enjoy his family and social life to the full, and he was always helping someone in trouble in very personal and practical ways."

Dr. Davidson is survived by his wife and only son.

Prof. R. M. GORDON

C. W. writes:

"It was a constant delight to meet and work with Gordon. For him the comic outlook was always near the surface, even in the intense seriousness of his work; he laughed a lot, and told with the greatest relish, but without any malice, his stories of the foibles of people he had known. He was always friendly, and his approach to people and events was affirmative. I think that life was fun to him; he certainly made it so to those of us who had the unforgettable good fortune to know him."

Notes and News

FOREIGN DOCTORS IN RHODESIA AND NYASALAND

OPPORTUNITIES for doctors previously unable to practise in the Federation of Rhodesia and Nyasaland are offered by the passage of the Medical Practitioners and Dentists (Amendment) Bill which had its third reading in the Federal Assembly on Aug. 14. Dr. D. M. Blair, Federal Secretary for Health, said on Aug. 12 that he hoped the new legislation would enable doctors and dental surgeons from Scandinavia, the Benelux countries, Western Germany, Switzerland, and Italy as well as Commonwealth countries to "come here and work under conditions which provide unrivalled opportunities for practice in an interesting and challenging situation."

Medical and dental registration in the Federation of Rhodesia and Nyasaland has so far been governed by the territorial laws which were in operation before federation.

In Southern Rhodesia the law provided for registration by a Medical Council which could prescribe certain qualifications as acceptable and leave others for consideration on individual application. But this law forbade the Council to register degrees and qualifications granted outside the Commonwealth.

In Northern Rhodesia and Nyasaland, where there are no medical councils, territorial legislation allowed the registrar to accept qualifications which were also acceptable in Britain, which in some respects is more restrictive than Southern Rhodesia in that some Canadian qualifications are excluded, and in other respects more liberal in that a few qualifications acceptable there are not acceptable in Southern Rhodesia.

The Medical Practitioners and Dentists (Amendment) Act will allow the territorial registering authorities to accept the names of doctors and dentists holding Commonwealth and foreign degrees which were formerly unacceptable. The principles underlying the new legislation are as follows:

(*a*) The standard of professional education shall not be lower than that of qualifications at present acceptable—in general the standard of qualifications at present awarded in Great Britain and Ireland.

(*b*) The qualification shall be registrable or otherwise legally recognisable for medical or dental practice in the country in which the school is situated.

(*c*) The applicant shall have an adequate knowledge of the English language.

All applicants will also have to satisfy normal immigration requirements.

PSYCHOLOGY IN RUSSIA

A QUARTERLY journal, *Problems of Psychology*,[1] which has been started under the sponsorship of the British Psychological Society, contains translations of selected papers from the U.S.S.R. publication *Voprosy psikhologii*—the first Russian journal to be concerned exclusively (since 1955) with psychology. Numbers 1 and 2, published together, contain 14 articles concerned mostly with studies of perception and intellectual development, but there is an unusual account by A. R. Luriia of years of study of a man with very great powers of memory. Clearly most of these Russian writers are closely familiar with Western work.

Society of Apothecaries of London

On Aug. 15 Mr. A. M. A. Moore was elected master of this society, with Mr. T. K. Lyle and Dr. Redvers Ironside as wardens.

The following diplomas have been granted:

M.M.S.A.—E. J. R. Rossiter.

L.M.S.S.A.—N. K. Coni, S. M. El Dardiry, P. M. J. Ephson, J. D. Fox, G. J. Lumsden, H. Morris, K. C. Ng, P. H. Rees, M. T. S. Roberts, C. C. T. Whaby, G. Van der Wilk, S. S. Woo, D. R. David, F. J. Husain, D. B. D. Jones, I. D. Morrison, T. A. J. Ogunbiyi, E. F. H. Parry, R. K. Saverimuttu, B. P. Krishnamurthy, S. M. Rau.

D.I.H.—S. L. Chadha, G. D. Chetty, D. D. Desai, S. Dobson, J. D. M. Holt, L. J. G. Morgan, W. D. O'Regan, R. Owen, D. A. Slattery.

1. Published by Pergamon Press, Headington Hill Hall, Oxford. £15 ($40) per annum. Single issues £4 ($12). The hon. scientific translation editor is N. O'Connor, PH.D., Institute of Psychiatry, Maudsley Hospital, London, S.E.5.

University of Cambridge

On Aug. 5 the following degrees were conferred:

M.D.—*A. P. C. Bacon, * W. McC. Edgar, * C. B. Mortimer, * E. W. Price, * Stanley Shaldon, * A. J. H. Tomlinson, E. B. Verney, L. G. Whitby.

M.B., B.Chir.—* D. J. Evans, * Neville Jankey, Frances R. Jordan, * W. J. Norman.

M.B.—* Sarah E. Bundey, Jennifer M. Charlton, M. J. Denham, R. H. Eleady-Cole, Suan Yew Lee, * Gwendolen D. Loft, Ian Phillips, * R. D. Pyrah, * M. T. S. Roberts, * Marian N. Sampson.

* By proxy.

International Pigment Cell Conference

This conference, sponsored by the New York Academy of Sciences, will be held from Oct. 11 to 14 in New York. Particulars may be had from the conference cochairmen, Dr. Vernon Riley and Dr. Joseph G. Fortner, Sloan-Kettering Institute for Cancer Research, New York, N.Y.

Asia and Oceania Congress of Endocrinology

This congress is to be held at the University of Sydney, New South Wales, Australia, from May 28 to June 2, 1963. Particulars may be had from the congress secretary, Dr. P. J. Claringbold, Department of Veterinary Physiology, University of Sydney.

World Federation of Neurology

An international symposium on enzymic activity in the central nervous system is to be held in Göteborg, Sweden, from June 18 to 21, 1962. Particulars may be had from Dr. G. B. Ansell, Department of Experimental Psychiatry, Medical School, Birmingham, 15.

Royal Medical Benevolent Fund

The 125th annual general meeting will be held at the house of the Medical Society of London, 11, Chandos Street, London, W.1, on Tuesday, Sept. 5, at 5 P.M. The Fund's office is at 37, St. George's Road, Wimbledon, S.W.19.

Role of Psychosomatic Disorder in Adult Life

A conference on this subject will be held, under the auspices of the Society for Psychosomatic Research, on Friday and Saturday, Nov. 3 and 4, at the Royal College of Physicians, Pall Mall East, London, S.W.1. Those wishing to attend should apply to the hon. secretary of the society, Dr. H. H. Wolff, 70, Harley Street, W.1.

National Association for Mental Health

A conference on the employment of the mentally disordered is to be held by the northern branch of this Association on Thursday and Friday, Oct. 26 and 27, in Harrogate. The speakers will include Prof. D. B. Bradshaw, Dr. R. C. Cunningham, and Dr. Robert McDonald. Applications for tickets (25*s.*) should be sent to the northern secretary of the Association, 9, Mount Preston, Leeds, 2.

Dr. P. W. Nathan is going to the U.S.A. at the end of this month as visiting professor of neurology in the University of Denver, Colorado.

On Saturday, Oct. 14, at 10 A.M., at the Royal Academy of Music, Marylebone Road, London, N.W.1, the Society for Music Therapy and Remedial Music is to hold a conference on music therapy in hospitals and hospital schools. Further particulars may be had from Miss Juliette Alvin, hon. secretary of the society, 6, Westbourne Park Road, London, W.2.

CORRIGENDUM: *Acute Leukæmia and Klinefelter's Syndrome.*—In the letter last week by Dr. Kemp, Dr. Stafford, and Mr. Tanner the 5th sentence in the 2nd paragraph should have read: "The erythroblast cytoplasm did not contain periodic-acid-Schiff-positive material."

Appointments

BAINES, G. F., M.B. St. And.: senior casualty officer, Newcastle upon Tyne hospital group, main duties at Newcastle General Hospital.

DAVIES, D. G. L., M.B. Lond., B.SC. Wales, F.R.C.S.: consultant general surgeon, East Glamorgan Hospital and Llwynypia Hospital.

JACKSON, R. H., M.C., B.M. Oxon., M.R.C.P.: consultant pædiatrician, United Newcastle upon Tyne Hospitals and Gateshead hospital group.

TRENHAILE, ARTHUR, L.M.S.S.A.: assistant M.O., Monmouthshire.